

GUIDE TO REPLACEMENT THERAPY FOR LOSS OF BLOOD OR PLASMA

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The efficacy of transfusion of blood and plasma for relief of shock has become well established. An important problem in replacement therapy is the amount of blood or plasma which is necessary for the individual patient. This depends primarily on two factors: (1) the amount of blood and/or plasma which was originally lost or which continues to be lost subsequent to the shock stimulus or as a result of additional shock stimuli, and (2) the extent to which the compensatory mechanisms of the body, such as vasoconstriction and hemodilution, can make up for the deficiency in blood volume. (Vasoconstriction attempts to adjust the size of the vascular bed to the remaining blood volume, and hemodilution endeavors to replace the loss of whole blood or plasma with tissue fluids.)

The effectiveness of the compensation for a reduction in blood volume depends to a large extent on the original condition of the patient as well as on associated injuries or subsequent therapeutic procedures. Dehydration renders the dilution mechanism less effective. Anemia places a limitation on the extent to which the body will tolerate loss of red cells, and hypoproteinemia may diminish the amount of loss of plasma which can be tolerated. An associated injury to the spinal cord or a subsequent spinal anesthesia will impair the vasoconstrictive mechanism in its attempt to render more effective such blood volume as is available for circulation.

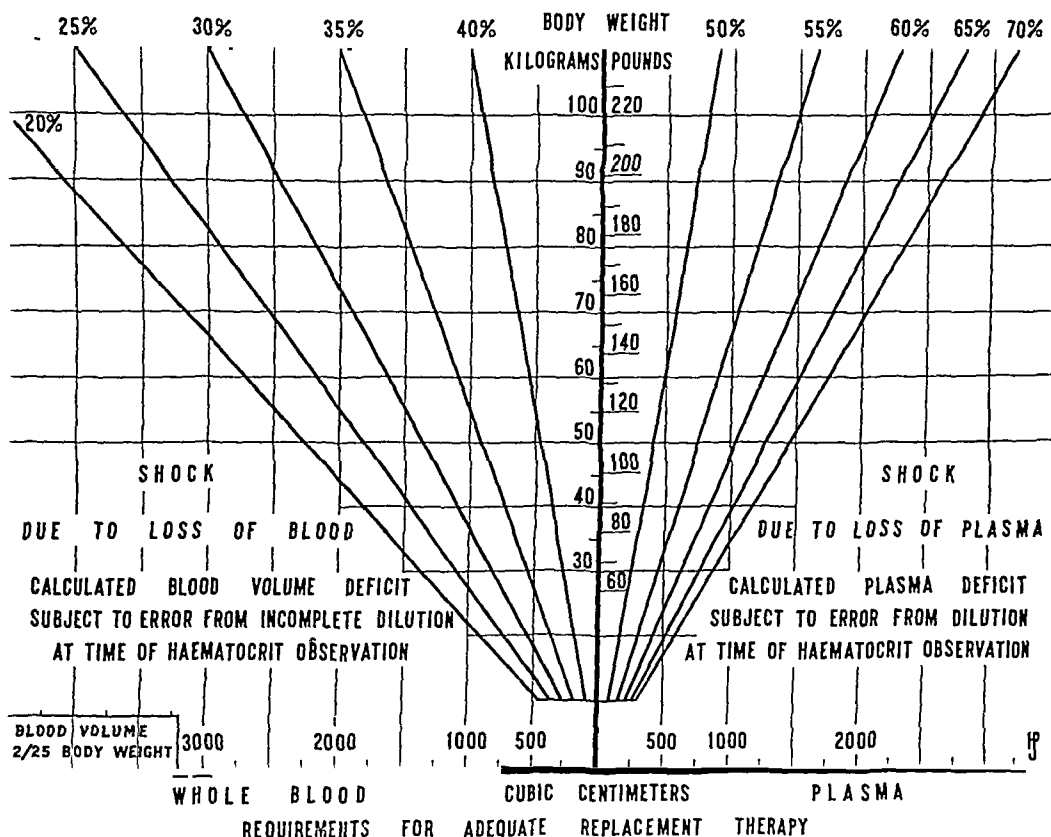
The complete evaluation of the replacement requirements of any one patient requires: (1) measurement of the blood volume, (2) estimation of the efficiency of the vasoconstrictive mechanisms and (3) analysis of the composition of the blood. Methods of determining blood volume are available for clinical use¹ but as yet require equipment not generally available in most hospitals. No reliable test for the efficiency of the vasoconstrictive mechanism has been worked out as yet, although utilizing direct examination of the blood vessels of the conjunctiva by a technic worked out by Knisely² may have possibilities. Much of the information which can guide one in the therapy of shock has to do with the composition of the blood. Considerable attention to this aspect has been drawn by Scudder.³

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Chicago.

1. Schafer, P. W.: Blood Volume Studies: A Review, to be published.
2. Knisely, M. H., and Bloch, E. H.: Microscopic Observation of Intravascular Agglutination of Red Cells and Consequent Sludging of the Blood in Human Diseases, *Anat. Rec.* 82:34, 1942; personal communication to the author.
3. Scudder, J.: Shock: Blood Studies as a Guide to Therapy, Philadelphia, J. B. Lippincott Company, 1940.

The most reliable index of the relative cell content of the blood is the hematocrit reading, or value for cell volume. The hematocrit provides an estimation of the extent to which dilution of the cellular elements of the circulating blood has occurred after loss of whole blood or the extent to which the blood has become concentrated after loss of plasma. From this information one can estimate the approximate deficit in blood volume. In some cases it may also be desirable to take into consideration the protein content of the plasma.

Various methods of estimating replacement requirements for shock due to loss of plasma have been devised. The formula of Harkins⁴ is relatively simple and is widely used. The formula of Elkinton, Wolff and Lee⁵ and the chart of Wolff and Lee⁶ offer a more complete analysis of the replacement requirements. The



To determine requirements for replacement of blood or plasma follow the diagonal line of the hematocrit reading to the point where it intersects the horizontal line of the patient's body weight, in either kilograms or pounds; then follow the vertical line down to the calibration of the required amount of blood or plasma on the bottom line of the chart.

methods of Black⁷ and of Berkow⁸ also deserve mention. These methods were designed principally for shock due to burns.

4. Harkins, H. N.: *The Treatment of Burns*, Springfield, Ill., Charles C Thomas, Publisher, 1942.

5. Elkinton, J. R.; Wolff, W. A., and Lee, W. E.: *Plasma Transfusion in the Treatment of Fluid Shift in Severe Burns*, *Ann. Surg.* **112**:150, 1940.

6. Wolff, W. A., and Lee, W. E.: *A Simple Method for Estimating Plasma Protein Deficit After Severe Burns*, *Ann. Surg.* **115**:1125, 1942.

7. Black, D. A. K.: *Treatment of Burn Shock with Plasma and Serum*, *Brit. M. J.* **2**:693, 1940.

8. Berkow, S. G.: *A Method of Estimating the Extensiveness of Lesions (Burns and Scalds) Based on Surface Area Proportions*, *Arch. Surg.* **8**:138 (Jan.) 1924.

In an attempt to furnish a simple guide to replacement therapy in shock due to loss of blood or loss of plasma the accompanying chart was constructed. It is based primarily on the hematocrit value and the body weight, the two variables which can be most easily determined under emergency conditions. The normal total blood volume was considered to be two twenty-fifths of the body weight in the light of clinical observations made by one of us (P. W. S.). The normal hematocrit reading was taken to be 45 per cent. Readings below 45 per cent reflect the extent to which the blood volume has been depleted by loss of whole blood and is being replaced by withdrawal of tissue fluids into the circulation. On the other hand, readings above 45 per cent reflect the extent to which the blood volume has been depleted by loss of plasma with resulting hemoconcentration.

When blood is lost, as in hemorrhage or by formation of a hematoma, the process of hemodilution may be slow. Therefore, the original hematocrit reading may not yet reflect the extent to which the blood has been depleted. Consequently the total amount of blood indicated on the chart on the basis of that hematocrit reading may be less than the amount which was originally lost and hence may not be adequate for complete replacement therapy. It does, however, constitute at least a good start toward adequate replacement. Subsequent hematocrit determinations after further dilution has occurred permit correction of the total amount of blood required for complete replacement.

In regard to the amount of plasma which is necessary after loss of plasma, as in burns, crushing injuries or contusions of soft tissues, the hematocrit readings also represent the minimum requirements, because any error on the part of the hematocrit in depicting the deficit in blood volume is due to dilution of the residual plasma by protein-poor tissue fluids. Therefore, for any given hematocrit reading above 45 per cent, regardless of the extent of dilution by tissue fluids, the chart indicates the minimum amount of plasma which will be required for replacement. In such a situation replacement by this amount of plasma of normal protein content at least represents a start toward adequate replacement, and subsequent hematocrit determinations will guide one in estimating the full requirements of plasma in the event of appreciable dilution of the residual plasma. Determinations of the protein content of the plasma are of additional help in estimating the deficit of protein. When facilities are available for such tests, one may make corrections in plasma requirements such as are presented in the chart devised by Wolff and Lee.

When both whole blood and plasma are lost, as in severe fractures or in burns complicated by hemorrhage, the hematocrit reading will not reflect the total deficit in blood volume to the same extent as when the preponderate loss is either blood or plasma. However, for deviations of the hematocrit value below or above 45 per cent that may be observed in such circumstances the chart still indicates the least amount of whole blood or plasma which will be appropriate for replacement. When subsequent changes in the hematocrit reading occur during the course of compensation or treatment, one may then make corrections in the estimate of the total replacement requirements until such time as the hematocrit value becomes relatively stable at 45 per cent.

SUMMARY

This guide to replacement therapy is presented as a simple means of evaluating the *minimum* requirements of blood or plasma for a patient who has suffered loss of blood or loss of plasma. It should be of particular value during the earlier phase of deficiency in blood volume, when clinical symptoms of shock have not as yet appeared.

LIGATION OF THE SAPHENOUS VEIN FOR VARICOSE VEINS

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In a time such as the present, with the entire resources of the nation mobilized for the successful conduct of war, it is particularly important that elective operations for the persons constituting the nation's manpower result in a maximum number of cures. Varicose veins of the lower extremities cannot be considered a major cause of disability,¹ but the impairment of efficiency of soldiers and workmen afflicted with them is readily apparent.

Even in a small station hospital such as this, patients are seen too frequently with recurrent or inadequately treated varicose veins. In many of the cases it is obvious that if a systematic examination and a proper plan of treatment had been followed a much more satisfactory result could have been obtained. Despite the numerous excellent papers which have been written on this subject,² the correct use and technic of ligation of the saphenous vein do not appear to be widely enough understood. Any surgeon who has had occasion to religate the saphenous vein at the saphenofemoral junction only a few months after the first operation can readily appreciate this.

The purpose of this discussion is not to review the pathogenesis, the physiology or the treatment of varicose veins, but is solely to emphasize the importance of proper technic for ligation of the saphenous vein. The tests for determining the competence of the saphenous valves at the fossa ovalis and for locating incompetent communicating veins are described in standard surgical textbooks.³ The tests used at this hospital are the Trendelenburg, Schwarz, Perthes, Harkins⁴ and Ochsner-Mahorner.⁵ Depending on the results, ligation at the saphenofemoral junction alone may be indicated, or a more extensive operation with multiple

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1. Of 19,923 registrants examined by Selective Service local boards, 531 had varicose veins, an incidence which represents a defect rate of 26.7 per thousand examined (Rowntree, L. G.; McGill, K. H., and Folk, O. H.: Health of Selective Service Registrants J. A. M. A. **118**:1223 [April 4] 1942).

2. Recent papers include: Barrow, W.: Physiologic Changes Associated with Varicose Veins and Their Correction, Arch. Surg. **45**:633 (Oct.) 1942. Harkins, H. N., and Schug, R.: The Surgical Management of Varicose Veins: Importance of Individualization in the Choice of Procedure, Surgery **11**:402 (March) 1942. Moore, S. W., and Knapp, G. M.: Varicose Veins, Ann. Surg. **115**:131 (Jan.) 1942. Payne, R. T.: The Scope of Operation in the Treatment of Varicose Veins, Brit. M. J. **2**:533 (Oct. 18) 1941. Sherman, R. S.: Varicose Veins: A Suggested Operative Procedure, California & West. Med. **57**:192 (Sept.) 1942. Symposium on Varicose Veins, Proc. Staff Meet., Mayo Clin. **16**:820 (Dec. 24) 1941.

3. Ferguson, L. K.: Surgery of the Ambulatory Patient, Philadelphia, J. B. Lippincott Company, 1942. Christopher, F.: Minor Surgery, Philadelphia, W. B. Saunders Company, 1938.

4. Harkins, H. N.: Individualization in the Surgical Treatment of Varicose Veins, Ann. Surg. **113**:1109 (June) 1941.

5. Mahorner, H. R., and Ochsner, A.: The Modern Treatment of Varicose Veins as Indicated by the Comparative Tourniquet Test, Ann. Surg. **107**:927 (June) 1938.

incisions for perforating veins may be required. But regardless of the extent of the operation, it is of primary importance that a standardized procedure be followed in ligating the proximal portion of the great saphenous vein.

Inadequate ligation is indicated by the finding of : (1) a palpable dilated vein at the fossa ovalis, (2) a positive result of the Trendelenburg test, (3) emptying of the dilated veins when the patient walks with a tourniquet at the fossa ovalis, (4) a small cutaneous incision and (5) most conclusively, an intact saphenous vein or dilated tributary at operation. If the foregoing evidences are present, it appears that at the first operation only the saphenous vein or a large tributary mistaken for it was ligated.

Three constant tributaries of the great saphenous vein near the fossa ovalis are usually described. These are the superficial iliac circumflex, the superficial epigastric and the superficial external pudendal vein. The medial and lateral superficial femoral veins are inconstant tributaries. Great variation in the number, size and location of the tributaries is known to occur. In my cases during the past few months, I have attempted to diagram accurately these variations, and even in the small number which I have recorded the extent of variation is marked. It is therefore my feeling that three requirements must be fulfilled before a complete ligation is done: (1) The great saphenous vein must be ligated close to the

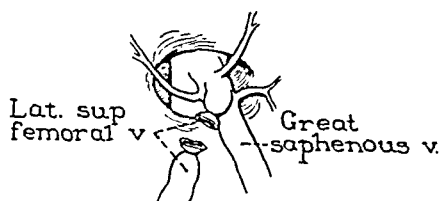


Fig. 1.—Ligated lateral superficial femoral vein which was mistaken for the great saphenous vein.

femoral vein; (2) a segment of vein at least 5 cm. in length must be removed, and (3) all tributaries in this segment must be separately ligated. If this is not done, a continuation or recurrence of the incompetency of the saphenous system at the fossa ovalis must be expected.

From the diagrams, it can be seen that if a small incision is made and the first large vein encountered is ligated, the main trunk or a large connecting tributary may be missed. This, of course, will result in failure to stop the backflow. For this reason, an arbitrarily selected length of 5 cm. of vein is removed and all tributaries ligated. The ligation should be close to the femoral vein, not only to decrease the possibility of thrombus formation with resultant embolism, but to avoid overlooking a tributary which empties at or near the saphenofemoral junction and connects with the saphenous vein below the incision in the middle or lower portion of the upper part of the leg. Heyerdale and Stalker⁶ state: "This is a situation which we have seen often and is perhaps the most frequent cause of recurrence following operation on the incompetent great saphenous vein."

The procedure is briefly as follows. After preparation of the skin and infiltration with procaine hydrochloride, an oblique incision from 4 to 5 cm. in length is

6. Heyerdale, W. W., and Stalker, L. K.: The Management of Varicose Veins of the Lower Extremities, Proc. Staff Meet., Mayo Clin. 16:827 (Dec. 24) 1941.

made, located parallel with and approximately 3 cm. below Poupart's ligament and with the lateral end over the femoral pulsation. (The incision is intentionally placed below the fossa ovalis, as moderate retraction will permit excellent exposure of this opening and such an incision will also permit the dissection to be carried more

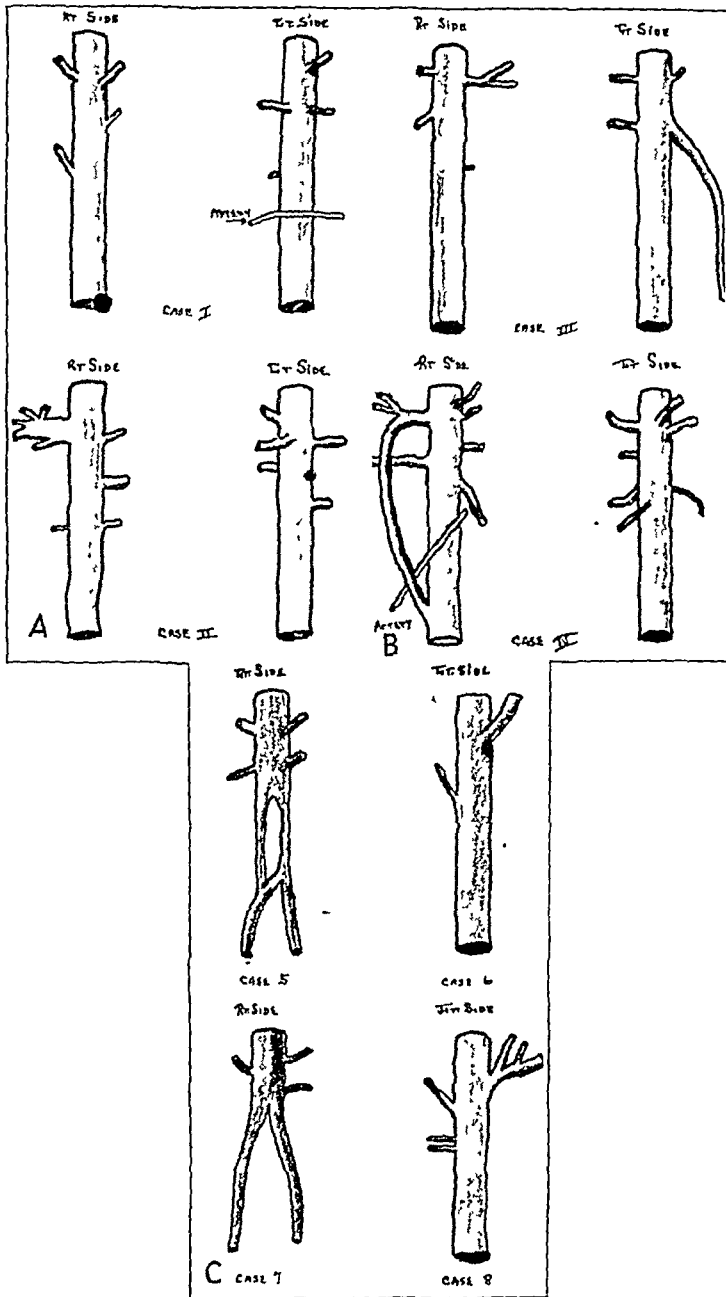


Fig. 2.—A, the length of vein diagrammed is roughly equivalent to the segment of vein removed at operation (7 or 8 cm.). The upper end is about 0.5 cm. from the femoral vein. B, the right side view for case 4 demonstrates how the backflow may continue through a connecting vein if the saphenous vein alone is ligated. C, cases 5 and 7 show how the ligation of one trunk may leave another tributary and therefore have no effect on the incompetence

distally.) The incision is carried down through the superficial fascia, where the great saphenous vein is found lying above the superficial layer of the deep fascia

(fascia lata) and usually in the medial half of the incision. The vein is isolated and divided between clamps. The dissection is carried superiorly to the saphenofemoral junction, each tributary being isolated, divided and ligated before the next is attacked. At the saphenofemoral junction, the saphenous vein is ligated as close as possible to the femoral vein, first with a single silk ligature and then with a transfixion suture of the same material. The portion of the vein distal to the ligature is excised. The dissection is then carried inferiorly, and by upward traction on the vein and downward traction on the edge of the wound a total of 5 to 8 cm. of vein is excised. A single ligature is placed about the inferior end of the vein. Enlarged lymph nodes should be avoided because of the oozing which occurs unless such a node is removed completely. At times a small artery (superficial external pudendal) may be found crossing the vein and this may be ligated if necessary. The superficial fascia and skin are closed with interrupted sutures of fine silk and a firm dressing applied.

The patient is urged to walk as soon as possible after the operation, and if necessary is helped to walk before six hours has elapsed. Walking is then required every seven hours.

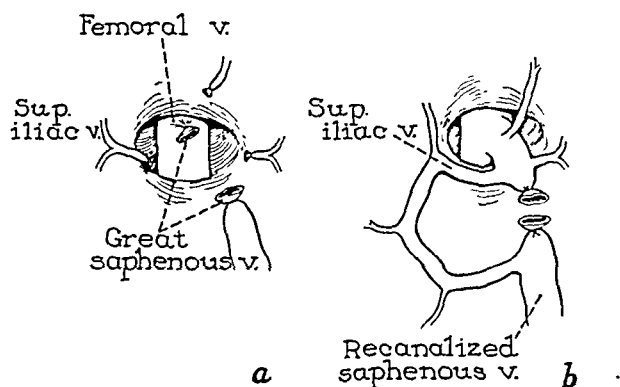


Fig. 3.—Diagrammatic appearance of: (a) proper ligation of the saphenous vein and its usual tributaries; (b) improper ligation of the great saphenous vein with disregard of its tributaries. The development of collateral circulation through the intact tributaries results in recanalization. (Figures 1 and 3 reproduced by permission of Drs. W. W. Heyerdale and L. K. Stalker.⁶)

Retrograde injection of sclerosing solution at the time of operation has been suggested by several authors, but I have not done it because (1) adequate thrombosis of the long saphenous system will occur occasionally after operation without injection, (2) leakage of the solution into the wound may result in unsatisfactory healing and (3) the resulting reaction in a patient sensitive to the sclerosing solution may cause prolonged incapacity.

SUMMARY

In the treatment of varicose veins of the lower extremities, ligation of the great saphenous vein at the fossa ovalis is an important part of the therapeutic plan. If success is to be expected, a complete operation must be done. This will include ligation of the saphenous vein close to the femoral vein, excision of at least 5 cm. of the saphenous vein and ligation of all tributaries of the excised segment.

SARCOMA OF THE STOMACH

A CLINICAL AND PATHOLOGIC STUDY

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In recent years there has been a considerable increase in the number of reports of cases of sarcoma of the stomach. It is the purpose of this study to add several cases to the literature and emphasize some of the pathologic features of the disease. The term "primary lymphosarcoma of the stomach" is confusing and requires clarification. It is generally agreed that lymphosarcoma is a systemic disease which may manifest itself in many different ways. If it appears in the stomach this is merely the site of local involvement. Unlike carcinomatous lesions, which form more or less definite patterns depending on the organ involved, lymphosarcoma is essentially the same regardless of the tissue in question. Like carcinoma it is malignant and spreads by continuity and contiguity and metastatically.

Morgagni¹ first described the condition in 1751. Sibley² in 1856, Bruch³ in 1847 and Cruveilhier⁴ in 1871 each reported cases. Virchow,⁵ in 1887, was the first surgeon to operate on a patient with gastric sarcoma. Fenwick,⁶ in a review of the subject, collected 60 cases reported up to 1900. He believed that in 53 of these the diagnosis was adequately proved. In 1913 Flebbe,⁷ basing criteria on autopsy observations, collected 157 cases. Forni,⁸ in the same year reported a collected series of 200 cases. In 1920 Haggard⁹ listed 244 cases, in 107 of which an operation was performed. D'Aunoy and Zoeller¹⁰ reviewed the literature in 1930, bringing the total to 335 cases. Madding¹¹ stated that 428 cases had been reported up to 1938. The considerable increase in reported cases in recent years must be attributed to better clinical and pathologic standards of diagnosis. This increase is further illustrated in that D'Aunoy and Zoeller¹⁰ reported 4 cases from the records of the Charity Hospital of Louisiana at New Orleans for the period 1906 to 1929. In the same institution during the period 1929 through 1942 there were 9 cases in which the diagnosis was proved by histologic study.

From the Departments of Surgery and Pathology, Tulane University, and the Charity Hospital of Louisiana.

1. Morgagni, cited by Hubeny and Delano.³⁰

2. Sibley, S. W.: Example of Multiple Fibrous Tumors, Tr. Path. Soc. London 7: 340, 1856.

3. Bruch, C.: Die Diagnose der bösartigen Geschwülste, Mainz, V. von Zabern, 1847.

4. Cruveilhier, cited by Forni.⁸

5. Virchow, cited by D'Aunoy and Zoeller.¹⁰

6. Fenwick, W. S.: Primary Sarcoma of the Stomach, Lancet 1:463, 1901.

7. Flebbe, G.: Ueber das Magensarkom, Frankfurt. Ztschr. f. Path. 12:311, 1913.

8. Forni, G.: Contributo allo studio del sarcoma primitivo della stomaco, Riforma med. 30:624, 1914.

9. Haggard, W. D.: Sarcoma of the Stomach, Surg., Gynec. & Obst. 31:505, 1920.

10. D'Aunoy, R., and Zoeller, A.: Sarcoma of the Stomach: Report of Four Cases and Review of the Literature, Am. J. Surg. 9:444, 1930.

11. Madding, G. F.: Lymphosarcoma of the Stomach with Particular Reference to the Reticulum Cell Variety, Proc. Staff Meet., Mayo Clin. 14:202, 1939.

Gastric sarcoma is generally agreed to constitute about 1 per cent of all malignant gastric tumors. Madding,¹¹ Ewing,¹² Pack and McNeer,¹³ Hesse¹⁴ and many others have cited this percentage. Mars and Kirshbaum¹⁵ reported an incidence of 1.5 per cent and Yates¹⁶ one of 2 per cent. From 1906 through 1941, 13 cases in which the diagnosis was proved were collected from the records of the Charity Hospital. Since in this same period malignant gastric lesions totaled 1,313, 0.99 per cent of these were sarcomas. The diagnosis of sarcoma of any variety or location was made in 1,373 instances. In 0.94 per cent of these cases the lesion was gastric.

The age incidence varies considerably. Chout¹⁷ reported a case he believed to be one of congenital lymphosarcoma of the stomach. Hunt¹⁸ operated on a 3 year old child with this disease, and Finlayson¹⁹ described the lesion in a 3½ year old child. The oldest patients reported on were Grosset's,²⁰ who was 85 years old, and di Giacomo's,²¹ who was 91. D'Aunoy and Zoeller¹⁰ cited the average age in their collected series as 41.6 years. Pack and McNeer¹³ found the average age to be 46 years, while Taylor²² found it to be 44.3 years. It is obvious, therefore, that the disease may appear at any age but that in general it is a disease of middle age, usually affecting persons a decade younger than the average patient with carcinoma.

The majority of reports emphasize a predominance in males (Taylor,²²) D'Aunoy and Zoeller,¹⁰ Pack and McNeer.¹³ Hochmann²³ stated that there is no difference in the sex incidence. Of the patients in our series of 9 cases, 4 were males and 5 females.

The cause of sarcoma of the stomach is not known. There has been no recent work to enlighten this phase of the disease.

The clinical picture varies considerably with the location of the lesion, its size and the presence or absence of ulceration and infection. Pain, which is often of the ulcer type, is the most common complaint. Epigastric pressure may be an early symptom, and frequently the first indication of the disease is the presence of an epigastric mass. A palpable tumor is present in 30 to 40 per cent of the cases. Nausea, vomiting, anorexia, loss of weight and weakness develop rapidly. The lesions seldom bleed, but tarry stools are occasionally noticed. Massive hemorrhage and perforation are rare. The presence of generalized lymphadenopathy indicates systemic involvement. Often low grade fever accompanies the condition but it is seldom of the Pel-Ebstein type until late in the course of the disease.

The diagnosis can be made only by microscopic examination. There are no characteristic symptoms, signs or laboratory data that justify a positive diagnosis. Haggard⁹ stated that hematemesis in a young person with or without severe pain

12. Ewing, J.: *Neoplastic Diseases*, ed. 4, Philadelphia, W. B. Saunders Company, 1940.

13. Pack, G. T., and McNeer, G.: *Sarcoma of the Stomach: A Report of Nine Cases*, *Ann. Surg.* **101**:1206, 1935.

14. Hesse, O.: *Das Magensarkom*, *Centralbl. f. d. Grenzgeb. d. Med. u. Chir.* **15**:550, 1912.

15. Mars, M., and Kirshbaum, J. D.: *Leiomyosarcoma of the Stomach with Perforation*, *Am. J. Roentgenol.* **44**:716, 1940.

16. Yates, J. L.: *Sarcoma and Myoma of the Stomach*, *Ann. Surg.* **44**:550, 1912.

17. Chout, L. K.: *Primary Sarcoma of the Stomach*, *Radiology* **34**:714, 1940.

18. Hunt, V. C.: *Partial Gastrectomy for Lymphosarcoma in Childhood*, *Ann. Surg.* **96**:210, 1932.

19. Finlayson, J.: *Case of Sarcoma of the Stomach in a Child Aged Three and One-Half Years*, *Brit. M. J.* **2**:1535, 1899.

20. Grosset, L. L.: *Le sarcome primitif de l'estomac*, *Presse méd.* **22**:221, 1912.

21. di Giacomo, G.: *Su due casi di sarcoma primitivo dello stomaco*, *Riforma med.* **31**:114, 1915.

22. Taylor, E. S.: *Primary Lymphosarcoma of the Stomach*, *Ann. Surg.* **110**:200, 1939.

23. Hochmann, A.: *Sarcoma of the Stomach*, *Lancet* **1**:362, 1940.

and a palpable tumor mass without obstruction may signify gastric sarcoma. Ritter²⁴ expressed the opinion that patients between 20 and 35 years of age with a large gastric neoplasm are more likely to have sarcoma than carcinoma. Indeed, these two conditions are frequently confused, and histologic examination of tissue from a patient operated on with a tentative diagnosis of carcinoma often proves the disease to be sarcoma. The gastric analysis varies with the location and extent of the lesion. A hypochromic, macrocytic anemia is the rule. Roentgenograms are not diagnostic. Several abnormalities of the rugae have been described, but as Chout¹⁷ and Archer and Cooper²⁵ pointed out, these are merely indications. Chout¹⁷ described flat tumors with smooth borders, pedunculated growths, isolated filling defects on the greater curvature with deep indentation or with a crater shadow in it and tumors on the greater curvature side of the fundus as suggestive of sarcoma. A number of writers have agreed with Schindler²⁶ that gastroscopic examination is an aid. In any event one must not hesitate too long to advise exploration when it is suspected that an ulcer or tumor in a patient of any age may be a malignant neoplasm. Time is just as important for the successful treatment of sarcoma as in that of carcinoma.

The pathologic classification of sarcoma in general has been and is still somewhat confusing. Ewing¹² mentioned three types when discussing gastric sarcoma:

1. Spindle cell myosarcoma
2. Miscellaneous round cell or mixed cell alveolar sarcoma
3. Lymphosarcoma
 - (a) Reticulum cell
 - (b) Malignant lymphosarcoma (small round cell)

Pack and McNeer¹³ in a recent paper clarified the problem further in an excellent table in which they described the histogenesis and the site of the lesion and the symptoms. They listed three main types:

1. Spindle cell sarcoma
 - (a) Neurosarcoma
 - (b) Myosarcoma
2. Lymphosarcoma
 - (a) Primary
 - (b) Generalized lymphosarcomatosis
3. Miscellaneous round cell or alveolar sarcoma; metastatic sarcoma, such as melanoma

They expressed the opinion that most so-called primary lymphosarcomas are of the reticulum cell type, and that relatively few, if any, are of the malignant lymphocytoma variety. Madding and Walters,²⁷ following Ewing's basic classification, differed in that they found an equal distribution of the two types. In addition these authors described cases of Hodgkin's sarcoma, leiomyosarcoma, fibrosarcoma and a mixed type. Roulet²⁸ described a tumor he called retotheliosarcoma, and Edling²⁹ pointed out that this is the same as reticulum cell lymphosarcoma.

24. Ritter, S. A.: A Case of Primary Lymphosarcoma Occupying Two-Thirds of the Fundus of the Stomach, *Am. J. Surg.* **47**:131, 1940.

25. Archer, V. W., and Cooper, G.: *Lymphosarcoma of the Stomach: Diagnosis and Treatment*, *Am. J. Roentgenol.* **42**:332, 1940.

26. Schindler, R.: *Gastroscopy*, Chicago, University of Chicago Press, 1937.

27. Madding, G. F., and Walters, W.: Lymphosarcoma of the Stomach, *Arch. Surg.* **40**:120 (Jan.) 1940.

28. Roulet, F.: Das primäre Retothelsarkom der Lymphknoten, *Virchows Arch. f. path. Anat.* **277**:15, 1930.

29. Edling, L.: Contribution to the Pathology and Clinical Picture of Reticulum Cell Sarcoma, *Radiology* **30**:19, 1938.

Hubeny and Delano³⁰ coined the term "retothel sarcoma," which is again the reticulum cell type.

Study of the gross pathologic anatomy indicates that the site of the tumor may be exogastric, intramural or endogastric. It may be a diffuse infiltrating lesion or a nodular tumor, or there may be multiple nodules invading all of the gastric wall. Other forms of gastric sarcoma are an infiltrating but limited lesion and a pedunculated, bulky, vascular tumor clearly demarcated from the gastric wall. Ewing¹² expressed the opinion that when the tumor grows beyond its blood supply ulceration results. According to Pack and McNeer,¹³ the tumor may invade the submucosa, stretching the mucosa, which then undergoes pressure atrophy and ulceration. Myosarcomas often attain enormous size and are usually subserous in their growth. Pack and McNeer¹³ described an exogastric myosarcoma which weighed 3,600 Gm. Such polypoid tumors may be intragastric or exogastric and usually arise on the greater curvature. When exogastric they usually spread between the layers of the great omentum. Brodowski³¹ described a tumor weighing 6 Kg. and containing 6 liters of fluid. Neurogenic sarcomas are often, though not always, associated with neurofibromatosis. The gastric lesion is similar in type to neurogenic lesions elsewhere and is often pedunculated or ulcerated and of low grade malignancy. On section the tumors generally are soft and sometimes cystic, with areas of firm, gray or reddish brown tissue and areas of degeneration and hemorrhage.

Madding and Walters²⁷ discussed the lymphatics of the stomach, which begin in the mucous membrane and extend through to the retroperitoneal glands. There are plexuses in the submucosa where the lymph follicles are situated. The central portion of each one (the secondary follicle) contains less mature lymphocytes. They are typical of lymphosarcoma in general. In reticulum cell sarcoma the lymph follicles are destroyed by large, pale cells with nuclei of bizarre configuration, round, oval or horseshoe shaped. The nucleoli are not prominent, and chromatin is diffusely dusted throughout the nuclear substance. The cytoplasm is eosinophilic. The cellular structure is loose, and small lymphocytes are present. The tumor is infiltrative, and tumor cells may be noted in the blood vessels. The gastric wall is destroyed, and regional metastasis may be present.

The malignant lymphocytoma, or small round cell type, involves the lymphoid tissue by infiltration of immature small lymphocytes. There is little fibrosis and no eosinophilia. Adjacent tissues may be invaded, and there may be an associated lymphatic leukemia.

Myosarcomas vary greatly from those of questionable malignancy, the extremely cellular myomas, to the anaplastic undifferentiated tumors of high malignancy. They are composed of spindle cells arranged in intertwining bundles or of large round cells. The cells may be very long, with finely fibrillar, acidophilic cytoplasm and hyperchromatic nuclei, often extremely large. Ewing¹² expressed the opinion that many so-called angiosarcomas and lymphangiosarcomas fall into this group.

Neurogenic sarcomas of the stomach are similar to those found elsewhere, being classifiable as sclerosing fibrosarcoma, spindle cell neurosarcoma and cellular anaplastic neurosarcoma. The structure may vary in the same tumor but in general the three classes correspond to the rate of growth.

The miscellaneous round cell or alveolar sarcoma tends toward alveolar grouping of the cells in some areas, while elsewhere the cells are scattered uniformly through-

30. Hubeny, M. J., and Delano, P. J.: Retothel Sarcoma of the Stomach, *Radiology* **34**:366, 1940.

31. Brodowski, W.: Ein ungeheures Myosarkom der Mägens nebst secundären Myosarkomen der Leber, *Virchows Arch. f. path. Anat.* **67**:227, 1876.

out the tissue and separated by a delicate stroma in which may run numerous small, thin-walled blood vessels.

In reality a sarcoma is a malignant tumor of connective tissue. Strictly speaking, then, malignant tumors of muscle, lymphoid tissue and pigment cells have no place in the classification. It has been the general custom, however, to include such tumors as lymphosarcoma in this classification, and until a better understanding of the basic tissues is had it seems best to apply clinical findings and past pathologic experiences in making up the grouping of sarcomas.

The prognosis in a case of gastric sarcoma depends entirely on the type of tumor and its location, extent and duration. The differentiated tumors, such as fibrosarcoma, leiomyosarcoma and neurogenic sarcoma, present a better prognosis than the more malignant undifferentiated myoma. A guarded prognosis is, of course, always the best. In general it may be said that the prognosis of sarcoma at the present time is better than that of carcinoma.

Treatment is of three types: surgical removal, irradiation (radium therapy, high voltage roentgen therapy or both) and a combination of operation and irradiation. A positive diagnosis is impossible without biopsy. If after exploration and diagnostic examination of a frozen section it is apparent that the lesion is not resectable irradiation alone should be employed. If the lesion recedes after irradiation, it may be advisable in certain selected cases to resect it at a later date.

REPORT OF CASES

CASE 1.—Mrs. A. T., a white woman 59 years old, was admitted to the Charity Hospital on Oct. 8, 1929, complaining of vomiting blood. On October 5 she had suffered attacks of dyspnea, severe abdominal pain and dizziness. On October 8 vomiting of a cup of blood was followed by a second emesis of a pitcher of blood. She had had frequent attacks of indigestion, constipation, dyspnea and edema of the ankles. No history of melena or loss of weight was recorded.

Examination revealed an extremely ill elderly white woman who appeared definitely anemic and did not respond well to questioning. There was general abdominal tenderness but no palpable mass. The temperature was 100 F., the pulse rate 104, the respiratory rate 22 and the blood pressure 108 systolic and 50 diastolic.

Laboratory studies revealed a red blood cell count of 2,700,000, a white cell count of 5,750 and a hemoglobin content of 55 per cent. The urine was normal, and the Wassermann reaction of the blood was negative.

The patient's course in the hospital was downhill, and she died on October 16.

Autopsy.—On the lateral wall of the stomach 3 cm. below the entrance of the esophagus and lying in the upper border of the greater curvature was an indurated ulcer 5 cm. in diameter. The borders were raised, and protruding from its center was a fungating mass of dirty gray, firm tissue, which divided it into compartments in which was found gray, glistening tissue. The stomach contained a thin, coffee-ground-like material.

The microscopic diagnosis was spindle cell sarcoma.

CASE 2.—L. C., a 39 year old Negro woman, was admitted to Charity Hospital on March 2, 1932, complaining of vomiting. She dated her illness back one year, at which time she noted fullness in the epigastrium following intake of food. Her mouth became sore, and her weight decreased from 135 pounds (61.2 Kg.) to 80 pounds (36.3 Kg.). Dietary treatment by her physician resulted in temporary improvement. In December 1931 vomiting began. This symptom progressed and the stools became watery and frequent, there being three or four a day, but no blood was passed. In February her vagina became sore. At the time of admission to the hospital she was extremely weak.

Examination revealed an emaciated Negro woman who had many dirty ulcerations of all mucous membranes. The blood pressure was 90 systolic and 68 diastolic, the temperature 98.6 F., the pulse rate 86 and the respiratory rate 20. A suggestion of a mass was present in the epigastrium. This mass was not tender and appeared to be movable.

Laboratory studies revealed an erythrocyte count of 3,000,000, a hemoglobin content of 45 per cent and white blood cell count of 7,000 with 60 per cent polymorphonuclear cells. The Wassermann reaction was negative. Gastric analysis showed no free hydrochloric acid

and a total acidity of 62 degrees. A series of roentgenograms of the gastrointestinal tract showed an extensive obstructive lesion in the region of the pylorus with dilatation of the stomach and large six, twenty-four and forty-eight hour gastric residues.

The patient was admitted to the medical ward with a diagnosis of pellagra. The roentgenograms suggested that carcinoma of the stomach was also present, and exploration was carried out. A subtotal gastric resection was done on April 6. The postoperative course was relatively smooth for four weeks, after which it was gradually downhill, with several episodes of psychosis. The patient died on June 27.

The tissue removed at operation consisted of the lower portion of the stomach, including the pyloric ring and the first centimeter of the duodenum. Just above the duodenum was a large ulcerated area, not much raised above the surface. However, the wall of the stomach was considerably thickened and indurated. The lesion was definitely a malignant tumor of the stomach, in a rather early stage, however, and inclined to be self limiting.

The microscopic diagnosis was lymphosarcoma, malignant lymphocytoma type (fig. 1).

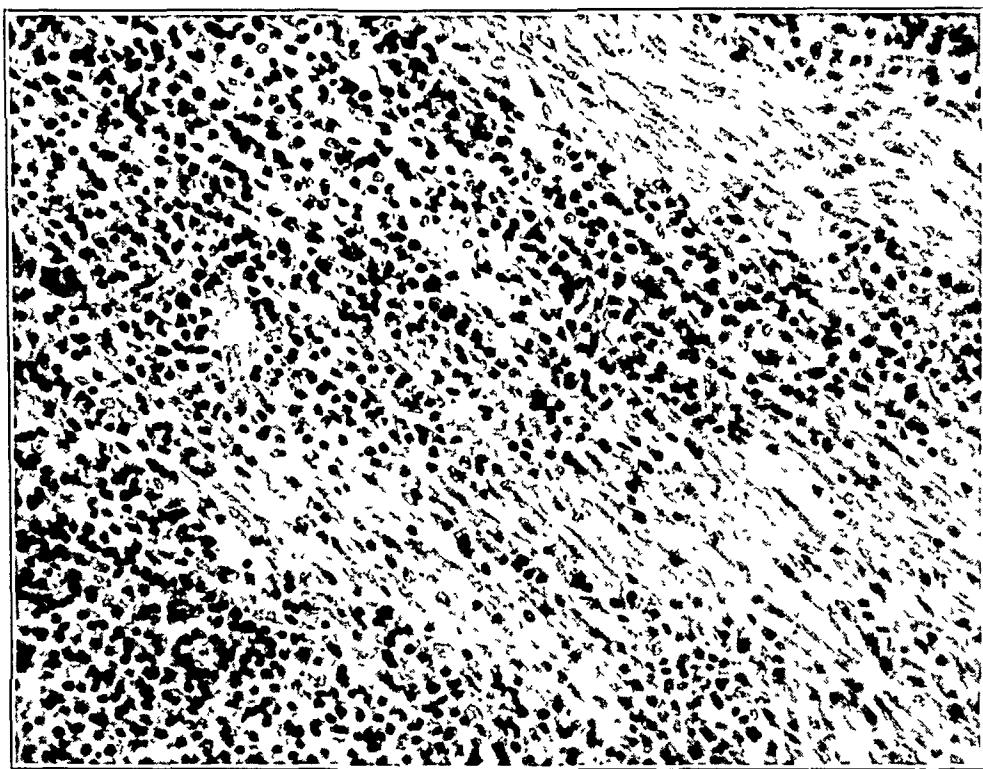


Fig. 1.—Photomicrograph of a section of the wall of the stomach, showing infiltration of muscular layers by neoplastic cells of malignant lymphocytoma, lymphosarcoma type. $\times 200$.

CASE 3.—A 50 year old Negro woman was admitted to the hospital on Oct. 10, 1933, complaining of pain in the left side. Five months prior to admission, in May 1933, a colicky pain aggravated by intake of food had developed in the left upper quadrant of the abdomen. The patient's physician tried various medications, but her symptoms were not relieved. He then noted a mass in the left upper quadrant of the abdomen and sent her immediately to the hospital.

On examination it was found that her temperature was normal, pulse rate 85, respiratory rate 20, and blood pressure 160 systolic and 100 diastolic. In the left upper quadrant of the abdomen there was a round mass, 15 by 15 cm., which was hard, movable and nontender and appeared fixed posteriorly.

Laboratory studies revealed an erythrocyte count of 4,325,000, a hemoglobin content of 75 per cent and a white cell count of 8,250. The Wassermann reaction, the blood chemistry and the results of urinalysis and phenolsulfonphthalein determinations were normal. Examination of the patient's stools revealed no blood or intestinal parasites. Roentgenograms of the

kidneys and bladder, including pyelograms, indicated normal conditions. A series of roentgenograms of the gastrointestinal tract demonstrated considerable displacement of the stomach downward, to the left and backward by an extensive tumor which also displaced the transverse colon downward. The most likely site of origin seemed to be the left lobe of the liver, and an amebic abscess was suspected.

When exploration was done on October 18 a tumor was found high in the upper left quadrant of the abdomen. It was adherent to the liver and transverse colon. The pedicle was attached to the anterior wall of the stomach and involved an area about 2.5 cm. in diameter. Excision of the tumor was accomplished, and the patient was discharged on November 10. No follow-up has been possible.

The pathologist's report stated that the specimen consisted of a lobulated tumor mass of bizarre appearance and fairly well encapsulated, although the capsule had been broken in many places, apparently during removal. The origin and anatomic structure of the tumor could not be determined. The tumor mass was extremely friable, and on section some areas were white and slightly firmer than others. Other areas had undergone hemorrhagic degenerative change. The lesion appeared to be a sarcoma.

The microscopic diagnosis was myxosarcoma.

CASE 4.—F. G., a 46 year old Negro man, was admitted to the hospital on Jan. 24, 1934, complaining of a lump in the stomach. In October 1933, the patient began having a feeling of discomfort in the stomach following meals. Home remedies relieved this feeling for a short period, but in November he began having a dull pain. His appetite diminished and he vomited frequently after eating. The vomitus never contained blood. In December he noted a mass in his stomach that was somewhat tender. The mass increased rapidly in size and he completely lost his appetite and became very weak and listless. He also noted occasional tarry stools.

Examination revealed an emaciated Negro man with a large, tender nodular mass extending from under the left costal margin into the upper right quadrant of the abdomen. The mass moved with respiration.

Laboratory studies revealed a red blood cell count of 3,770,000, a hemoglobin content of 55 per cent and a white cell count of 9,000. The Wassermann reaction was negative. Gastric analysis revealed no free acid and a total acidity of 9 degrees. Tests for occult blood gave positive results. A series of roentgenograms of the gastrointestinal tract showed a large tumor involving the prepyloric region of the stomach and the lower portion of the fundus. There was over 50 per cent gastric retention at six hours. The colon showed no evidence of pathologic change.

On Feb. 2, 1934, exploration was done and the lesion was discovered to be an extensive malignant tumor of the stomach with metastasis. Resection was not possible. The patient died on February 22, after a cerebral accident.

Significant observations at autopsy were limited to the brain, where embolism and necrosis had occurred, and to the gastrointestinal tract. The stomach was involved in a large mass of adhesions including the liver and the duodenum. When the stomach was opened a peculiar lesion apparently involving the mucosa was found. The wall of the stomach was not greatly thickened, and there was no induration of the tumor, which was flat. There were small ulcerations over approximately one third of the pyloric portion of the stomach. On the serosal surface of the stomach there were several small nodes which on section were white, watery and glassy and apparently sarcomatous. No further metastatic phenomena could be demonstrated. The duodenum was not involved.

On microscopic examination sections taken through the stomach showed a diffuse infiltration throughout the layers with small round mononuclear and multinucleated cells undergoing all stages of mitosis. The cells were definitely malignant and had the appearance of lymphosarcoma of the malignant lymphocytoma type.

CASE 5.—Mr. C. S., a 58 year old white man, was admitted to Charity Hospital on June 6, 1935, complaining of weakness, which had been gradual in onset over a period of four years. He also noted dyspnea, palpitation, vertigo, and a loss of 17 pounds (7.7 Kg.) in weight in one month. His appetite remained good.

Examination revealed an anemic-appearing man, with a lemon yellow tinge to the skin and evident pallor. The liver was palpable 2.5 cm. below the costal margin.

Laboratory studies revealed an erythrocyte count of 1,955,000 and a hemoglobin content of 45 per cent. Occult blood was present in the stools and gastric contents. Free hydrochloric acid was 53 degrees and total acid 86 degrees. The Wassermann reaction was negative, and the urine was normal. A series of roentgenograms of the gastrointestinal tract showed a prepyloric filling defect in the stomach. There was no six hour gastric residue, and no pathologic changes were observed in the colon.

After adequate preparation a subtotal gastric resection was done, and the patient was discharged in good condition on August 8.

The specimen submitted to pathologic examination consisted of two flat pieces of tissue on a portion of stomach wall with attached mesentery containing fat, which had been previously sectioned. The ulcer measured 1.5 cm. in diameter. It had a smooth surface, and there was considerable induration of the edges. There was a lymph node attached, which on section was smooth and pink.

The microscopic diagnosis was neurosarcoma (fig. 2).

The patient returned on Aug. 25, 1940, complaining of a mass in the abdomen. This was first noted in April and had gradually increased in size. No other symptoms were recorded.

On examination the mass was palpated in the midline at about the level of the umbilicus. It was 15 cm. in diameter, firm and not movable.

Laboratory studies revealed an erythrocyte count of 5,000,000 with a hemoglobin content of 90 per cent. The Wassermann reaction was negative, and the results of urinalysis and of

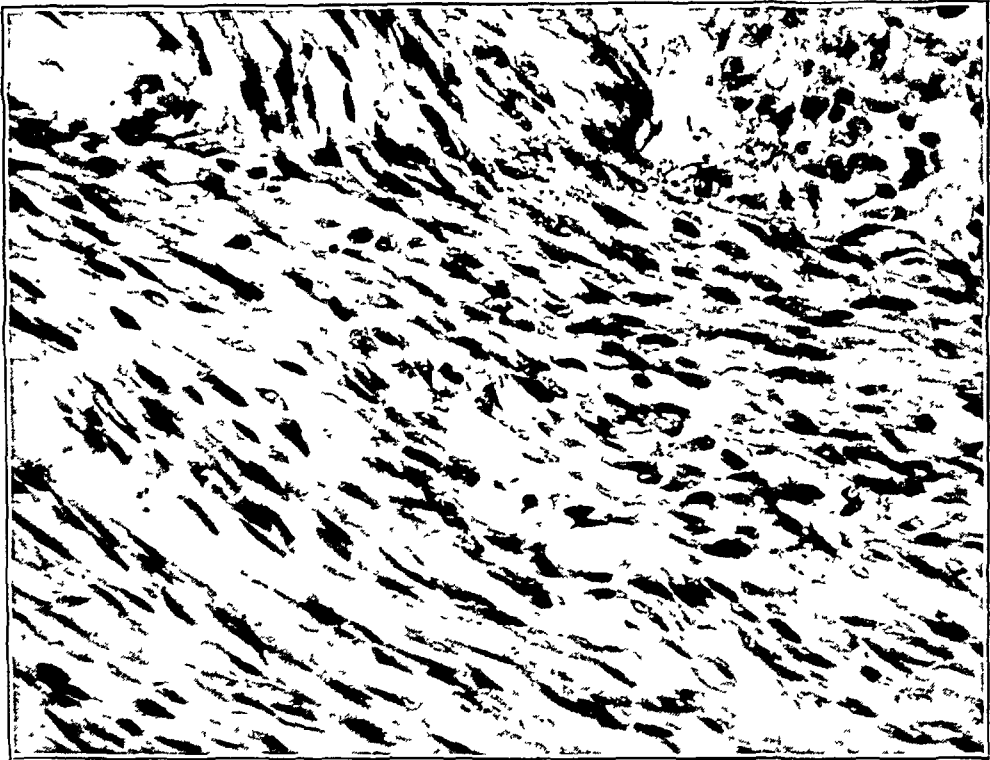


Fig. 2.—Photomicrograph of neurosarcoma of the stomach, showing spindle-like cells with anaplastic, deeply staining nuclei and an ample amount of cytoplasm, in columnar arrangement. $\times 200$.

chemical studies of the blood were normal. Roentgenograms of chest, pelvis and abdomen were negative. A series of roentgenograms of the gastrointestinal tract showed a normally functioning stoma. No evidence of recurrence was noted in the stomach. There appeared to be a large mass displacing the hepatic flexure of the colon downward.

Exploration on September 7 revealed a large tumor mass, approximately 10 cm. in diameter, in the retroperitoneal space. It pushed the transverse colon anteriorly so that it was flattened. By careful dissection the peritoneum over the mass was opened and in an attempt to isolate the tumor a portion of the capsule ruptured. A large amount of degenerated material was evacuated. The capsule was imbricated. The pathologist's report stated that the specimen consisted of a mass of tissue measuring 17 by 11 by 5 cm. It was soft and reddish brown. It was noted that here and there hemorrhages had completely replaced the substance of the tumor. Microscopic examination of the tissue revealed it to be a neurosarcoma similar to the previous growth. The patient made an uneventful recovery and was discharged on September 23. He was to return for some palliative high voltage roentgen therapy, but he failed to do so.

On March 8, 1942 he returned, stating he had been perfectly well until February. At this time he noted several episodes of nausea and vomiting. His abdomen began to swell and became painful. There was considerable loss of weight.

Examination revealed an anemic, poorly nourished white man with a distended abdomen. The abdominal veins were abnormally prominent, and shifting dullness and a fluid wave were present.

Laboratory studies revealed a red cell count of 3,500,000 and a hemoglobin content of 60 per cent. The white cell count was 7,800, with 62 per cent polymorphonuclear cells. The results of urinalysis and of chemical studies of the blood were within the normal range. Roentgenograms of the abdomen and the chest showed no evidence of pathologic conditions. On two occasions paracentesis was done, 1,000 cc. of bloody fluid being removed each time. Examination of this fluid failed to reveal any tumor cells. When the abdomen was flat, it was possible to palpate numerous nodules, some fixed and some movable. It was not deemed advisable to give palliative high voltage roentgen therapy because of the relatively poor response of neurosarcoma to such treatment. The patient was discharged on March 21 to return for additional paracenteses when needed. To the time of writing he has remained fairly comfortable.

CASE 6.—A. W., a 43 year old white man, was admitted to Charity Hospital on June 2, 1936, complaining of pain in the stomach. On May 14, after he had drunk a pint (475 cc.) of cold raw milk, he felt a severe pain in the stomach and his abdomen became distended. Thereafter eating was invariably followed by pain and bloating, relieved at times by sodium bicarbonate. He had not vomited.

Examination revealed a tender, painful abdominal mass about 6 cm. in diameter and movable. There was a small, hard nodule in the subcutaneous tissue just above the umbilicus.

The Wassermann reaction was negative, and the results of urinalysis and of the Aschheim-Zondek test were normal. A series of roentgenograms of the gastrointestinal tract showed an ulcer crater in the prepyloric region of the stomach. At six hours there was no gastric retention, the meal resting in the terminal portion of the ileum and the ascending colon.

On June 16 exploration revealed an extensive carcinoma which infiltrated the entire posterior wall of the stomach from the fundus to the pylorus. It was impossible to resect the lesion. The small nodule in the subcutaneous tissue as well as a portion of the gastric lesion was removed for study. Microscopic examination of this tissue revealed lymphosarcoma, reticulum cell type.

CASE 7.—H. E., a white man 67 years old, was admitted to the Charity Hospital on Oct. 26, 1939, complaining of "stomach trouble." For six months he had been having cramplike pain aggravated by intake of food. Constipation and tarry stools had been noted for a similar period, and there had been a loss in weight of 50 pounds (22.7 Kg.).

Examination revealed an emaciated, elderly white man with a distended, diffusely tender abdomen. The veins over the abdomen were tortuous and prominent. A tender, movable mass 5 cm. in diameter was present in the left lower quadrant. The liver was palpable 10 cm. below the right costal margin and was nodular.

Laboratory studies revealed an erythrocyte count of 3,500,000, a white cell count of 8,500 and a hemoglobin content of 70 per cent. The Wassermann reaction was negative and the results of urinalysis were normal. The icterus index was 14.5. A series of roentgenograms of the gastrointestinal tract showed a constant filling defect in the upper third of the stomach. At the end of six hours there was a trace of gastric retention.

The patient's course in the hospital was downhill, and he died on November 9. At autopsy a large mass, 11 cm. in diameter, was found in the fundus of the stomach. There was extensive infiltration of the entire gastric wall, so that the whole stomach presented considerable thickening, induration and narrowing of the lumen. There was a massive extension of the tumor tissue to the lymph nodes on the lesser and the greater curvature of the stomach, producing several large, extrinsic nodules of the tumor tissue, one of which extended into the notch of the spleen. There were a large nodule of tissue in the inferior surface of the left side of the diaphragm and a similar infiltration on the superior surface, which was not, however, adherent to the inferior surface of the lung. On the anterior surface of the stomach there was a necrotic perforation 1.5 cm. in diameter. The edges were indurated and grayish green.

Microscopic Examination.—Sections through the tumor tissue showed it to be composed of many small round cells lying in a network of skin strands of fibrillar connective tissue. Many of the cells were pointed. The nuclei were round and hyperchromatic and the cytoplasm was scant. Throughout the tumor tissue were scattered a number of larger cells which had large, oval nuclei and homogeneous pink-staining cytoplasm. A number of these cells had irregular nuclei. The impression was that the tumor was a lymphosarcoma of the stomach, malignant lymphocytoma type.

CASE 8—Miss G. P., a 70 year old white woman, was admitted to Charity Hospital on March 12, 1939, complaining of "hemorrhage from the rectum." The history obtained from her family consisted merely of the statement that she had had a large hemorrhage from the rectum.

Examination revealed a comatose, poorly nourished, elderly white woman. There was edema of the face and lower extremities.

She was given a transfusion of 500 cc. of whole blood but died the day after her admission to the hospital.

At autopsy the stomach contained a large amount of coffee-ground-like material. A nodule measuring 2.5 cm. in its greatest diameter was found in the anterior wall. The mucosa over the nodule was ulcerated and contained a thrombosed vessel. On section the nodule appeared pale gray and soft, except for a small portion which was firm. The heart was enlarged and dilated and there was complete consolidation of the lower lobe of the right lung. Microscopic sections through the neoplasm within the wall of the stomach revealed a whorled mass of spindle-shaped cells

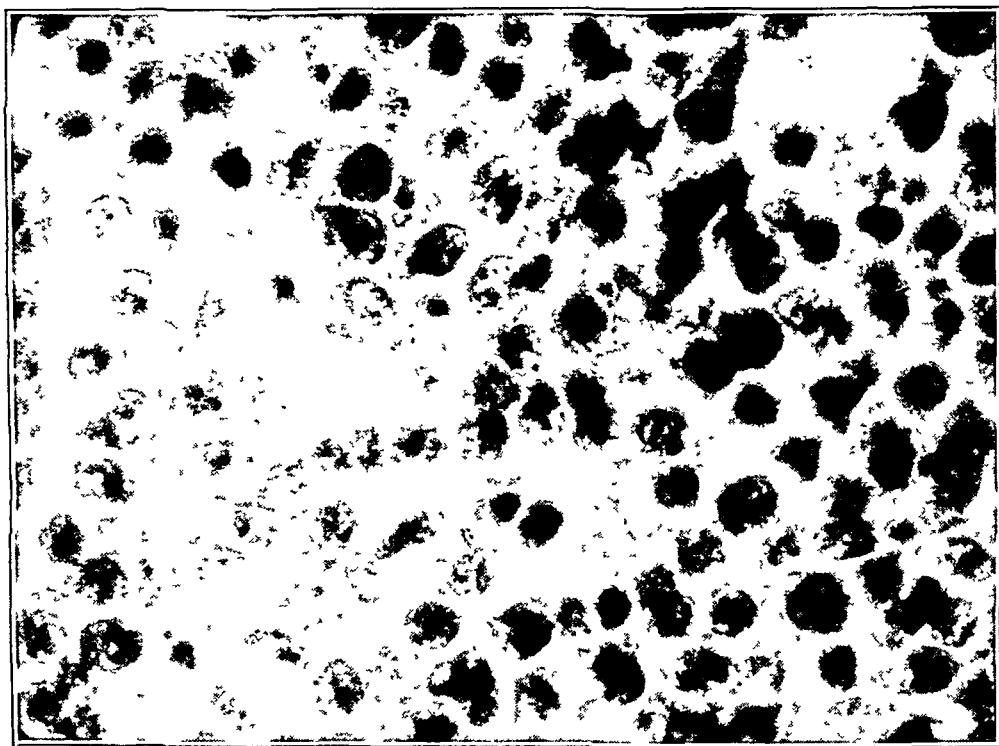


Fig. 3—Photomicrograph of malignant lymphocytoma, reticulum cell type, of the stomach. The cells are of large size, with prominent, vesicular nuclei, some appearing extremely anaplastic, and scanty amounts of cytoplasm. $\times 400$

situated within the muscularis. A few figures were present. The impression was that the lesion was a leiomyosarcoma of the stomach.

CASE 9.—W. N., a white man, aged 61 years, was admitted to the hospital on Dec. 29, 1939, complaining of "stomach trouble." In June he noted cramplike pain on eating, associated with vomiting. Later he noticed a small mass in the epigastrium, which gradually increased in size. He never vomited blood or passed blood by rectum.

Examination on admission revealed a cachectic elderly white man, very weak and pale. His abdomen was distended by a large mass. A rectal shelf was palpable.

The patient's course was rapidly downhill. He died on Jan. 5, 1940. At autopsy 2,000 cc. of serosanguineous fluid was found in the peritoneal cavity. The omentum could not be identified as such, for it was completely replaced by a mass of reddish gray, friable nodular tissue. The mesenteric lymph nodes were slightly enlarged, and the cut surfaces showed no neoplastic invasion. The wall of the stomach measured 2.5 cm. in thickness in the pyloric portion. The rugae were absent, and the mucosa was brownish red with gangrenous areas

1 to 2 cm. in diameter. On the anterior surface of the stomach was a mass 15 by 11 by 3 cm., which was reddish gray, firm and friable. The mass and the stomach weighed 1,350 Gm. The rectal wall was infiltrated by similar tissue. The lymph nodes in the region of the stomach were infiltrated with tumor tissue. Microscopically the mucosa of the stomach was infiltrated by lymphocytes. The submucosa and muscularis were infiltrated and had been replaced with tumor cells similar to those found in the tumor mass. The cells were small round cells with scant cytoplasm and large, dark-staining, vesicular nuclei. The connective tissue stroma was extremely scant. A few dilated capillaries traversed the tumor mass. The impression was that the lesion was lymphosarcoma, reticulum cell type.

CASE 10.—Mrs. L. H., a white woman 31 years old, was admitted to Charity Hospital on Jan. 17, 1941, complaining of "vomiting." For six months she had been vomiting, at first only occasionally and later three or four times weekly. She had lost 15 pounds (6.8 Kg.) in this time and had a very poor appetite. For the past two months she had had a dull burning pain behind the sternum.

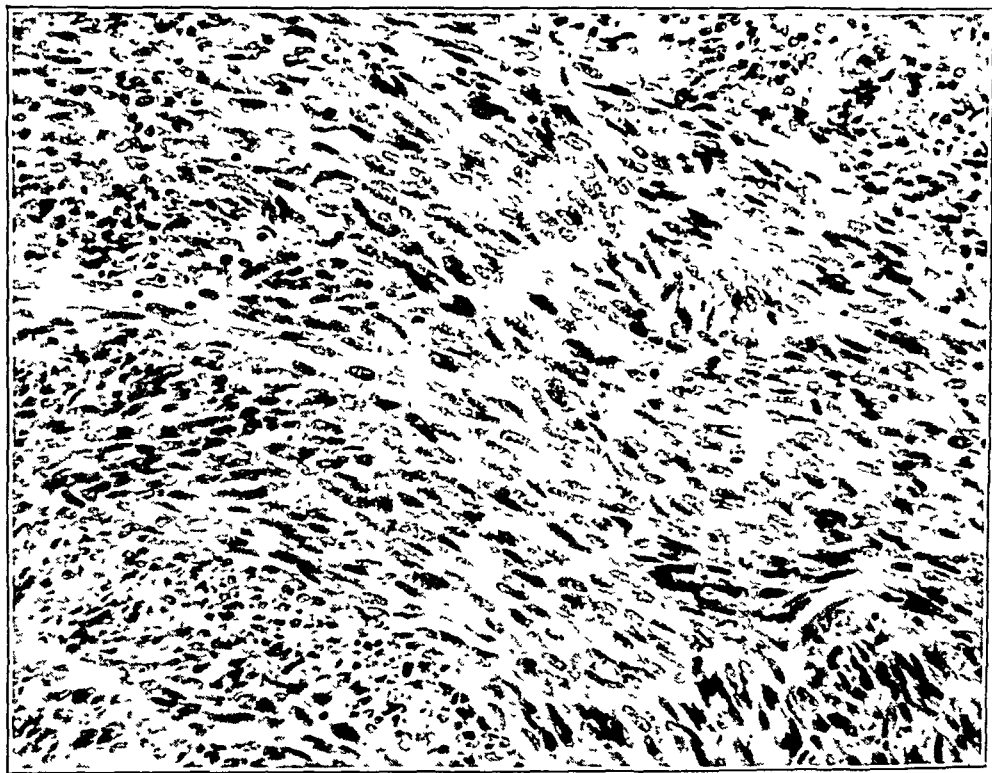


Fig. 4.—Photomicrograph of leiomyosarcoma of the stomach. The cells are spindle-shaped and arranged in whorls. Some are shown cut longitudinally, while others are cut transversely, giving them a spherical appearance. $\times 200$.

On examination she appeared normal except for fairly far advanced emaciation. Complete laboratory studies revealed an erythrocyte count of 4,400,000, with a hemoglobin content of 60 per cent and a white cell count of 10,300. The Wassermann reaction was negative and the results of urinalysis, complete chemical study of the blood, examination of the stools, and determination of the basal metabolic rate were normal. Roentgenograms of the gastrointestinal tract as well as of the chest and skull appeared normal. Gastric analysis revealed achlorhydria.

The patient's course in the hospital was uneventful, with no change in her condition other than relief of the intestinal burning by dietary measures. She was discharged on March 1 and told to return on March 31. She returned on this date to the medical service, where another gastrointestinal roentgenogram was taken, which showed a constant filling defect in the upper two thirds of the stomach. It was thought that the lesion was probably due to carcinoma. A roentgenogram of the chest as well as two Wassermann tests and an electrocardiogram did not afford any evidence of disease. The patient was prepared for operation,

and a total gastrectomy with esophagojejunostomy and enteroenterostomy was performed. It was necessary to remove the spleen because of damage to the splenic artery. Because of the suspected infiltration and adhesions a portion of the left lobe of the liver and the tail of the pancreas were also removed. The postoperative course was stormy, and death from peritonitis occurred on the sixth day, May 2, 1941.

The report on the tissue removed at operation was as follows:

The specimen consisted of a stomach, a spleen and two portions of liver. The stomach was complete. There was a small portion of duodenum attached to one end, which measured 2 cm. in length. The terminal end of the esophagus was also included. The proximal two thirds of the stomach on its anterior wall was injected, and occasional small fibrous adhesions were attached to it. The distal third was lined with rather smooth pale yellow serosa. There were two openings in the anterior surface of the stomach along the greater curvature. The more proximal one, which was located 3 cm. from the esophageal opening, measured 2.5 by 1 cm. The more distal one, which was located 6 cm. beyond the first, measured 3.5 cm. in diameter. However, the edges of these two openings could easily be brought together. The larger one had a portion of the liver attached to the pedicle. The piece of liver measured 5 by 2.5 by 1.5 cm. The liver was dark brown and friable and was attached rather intimately to the pedicle which covered the large opening. There was a moderate amount of gastrohepatic ligament attached. Within the gastrohepatic ligament just beneath the esophagus were several moderately firm grayish white lymph nodes varying from 0.5 to 1 cm. in diameter. They extended down for a distance of 3 cm. from the esophageal opening. Several cotton sutures were also noted on the gastrohepatic opening. The omentum attached to the greater curvature of the stomach varied in length from 1 to 2 cm. There were fibrous adhesions attached to it. In general the omentum was firm and coiled up on itself. Along the distal third of the greater curvature there were approximately six other lymph nodes varying from 0.5 to 1 cm. in diameter. These were pinkish gray, and the largest one showed an area which appeared to be well demarcated from the surrounding lymphoid tissue and measured 4 mm. in diameter. The mucous membrane throughout its entire length was injected and showed large areas of hemorrhage within the mucosa, especially in the midportion. In the fundal portion there was considerable ulceration, which extended in irregular fashion throughout approximately two thirds of the stomach and entered the body of the stomach. The intervening mucosa was polypoid in appearance. Some of the polypoid structures had flat tops. Others were dark red and elevated and varied from 1 cm. to 2 cm. in diameter. The wall of the stomach was moderately thickened, especially in the proximal two thirds. There was a certain amount of induration in this portion of the stomach. The distal portion was soft and pliable. There was another portion of the liver present, which was free and measured 6.5 by 2.5 by 1 cm. It was friable and reddish brown. The spleen measured 10.5 by 3.5 cm. The capsule was smooth except in the region of the pedicle, where there were three lacerations extending outward for a distance varying from 1.5 to 2 cm. and involving the capsule. On section the spleen was moderately firm. The splenic capsules were prominent. There was no invasion of fibrous tissue. The pulp was reddish brown.

The microscopic diagnosis was lymphosarcoma of the stomach, reticulum cell type, with metastasis to lymph nodes of the greater curvature.

SUMMARY

The subject of gastric sarcoma in general is briefly reviewed, and the incidence, clinical picture, pathology, prognosis and treatment are discussed. Ten previously unreported cases from the records of the Charity Hospital of Louisiana at New Orleans are presented.

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TREATMENT OF ACUTE CHOLECYSTITIS

A SUGGESTED TWO STAGE TREATMENT

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The controversy over the treatment of acute cholecystitis seems to have produced no definite agreement. This is partly because the conclusions and deductions of the many analytic studies are based on variable and inconstant factors. This paper is an attempt to find a common denominator for these factors and to place the problem, from both the etiologic and the therapeutic viewpoint, on a more solid pathologic basis. Such a state is desirable in view of the increasing consciousness that serious complications are more common than was formerly believed (empyema of the gallbladder, pericholecystitis, fistula formation, gangrene, perforation and such conditions).

The prevailing discussions do not, nor does this one, concern the general treatment, on which all physicians agree—namely, that the patient must be carried over the immediate dangers with the greatest assurance of safety. Rather, they concern the method by which this should be accomplished—i. e. medical therapy, which is conservative, or surgical therapy, which may be either radical or conservative. The majority will agree that in many instances a major curative surgical procedure can be carried out with more safety, less technical difficulty and less shock-precipitating trauma after the acute manifestations have receded (e. g. edema, congestion, localized necrosis, vascular thrombosis, lymphangitis, infection, hepatitis and suppuration)—if these conditions do recede, and if the resulting pericholecystic pathologic changes do not predispose to too much trauma when operation is done, and if the patient does not die as a result of the acute attack.

The possibility of a happy medium, a combination of the forms of therapy, seems to have been forgotten. This is due to several factors, the recognition of which will make one consider this condition with more deliberation. These factors are, principally: (1) failure to recognize acute cholecystitis as the consequence of an acute obstruction in an abdominal tube the distal end of which is closed (other causes of obstruction are recognized, but they are, for practical purposes, uncommon); (2) failure to recognize it as a progressive disease in itself as well as a most important step in the progression of chronic cholecystitis and its complications (i. e., progressive if an active effort is not made to prevent it); (3) failure to classify it as early or late according to the age of the pathologic changes rather than the age of the symptoms; (4) failure to consider the age of the patient. The older the patient, the greater is the likelihood that extracystic disease is present and that cardiovascular and renal disease may precipitate serious complications. Hence the physical status of the patient determines, in some degree at least, the treatment.

Acute cholecystitis is a symptom of an acute obstruction of the cystic duct. This is the fundamental pathologic condition.¹ Acute cholecystitis is, therefore, an end result, and its occurrence in a patient in or past the forties is presumptive

1. Macdonald, D.: The Postural Treatment of Biliary Colic: Its Relationship to Acute Cholecystitis, *Am. J. Digest. Dis.* **10**:138 (April) 1943.

evidence that extensive disease probably exists throughout the biliary system as well as in the gallbladder proper. Curative treatment will, consequently, be more than just the usual correction of an obstruction and possibly the removal of the nonviable part; it must also concern the associated and complicating condition (which involve the pancreas, liver, common duct and other organs). Hence the decision regarding the type and the timing of such treatment cannot always be based on statistics compiled after studying the records of patients operated on, or not operated on, so many hours after such and such an occurrence. This statement is further supported by the following facts: (a) Just as in all disease processes there is no definite or reliable correlation between the onset of the original pathologic changes and the first appearance of clinical complaints, so there is none in acute cholecystopathy. Pathologic changes may progress while the clinical symptoms and signs regress. In other words, the gravity of the clinical picture is never a reliable guide to the seriousness of the disease process. Hence such a word as "early," "late," "deferred" or "immediate" as a qualifying adjective for "operation" has little meaning from a pathologic viewpoint. (b) In such statistics "operation" means only that surgical intervention has been performed, and it does not always refer to any particular type, although cholecystectomy predominates. (c) Reference is rarely made to the anesthetic agent or to the anesthetist, and both these factors have more than a little influence on the outcome of any operation, whether it is a tonsillectomy or a total gastrectomy. (d) The threshold for pain and the constitutional stability of the patient are among the most inconsistent and variable factors in medicine, and these factors cannot be evaluated in large groups of patients. Therefore, in disease of the gallbladder of recent and acute onset, statistics should never completely influence the decision regarding therapy, because a decision can be made only on the case at hand, and the best decision can be made only if the actual and potential pathologic pictures are thoroughly understood and clearly visualized in relationship to the physical status of the patient. The latter point is the foundation on which the decision must be based, whether medical or surgical treatment is indicated. Patients cannot always be classified as surgical or medical on such variable bases as the number of hours they have felt sick and the number of hours they have been confined to a hospital bed. At any rate, such bases cannot be taken as standards. There must be a more constant criterion on which to base treatment. This is the cause producing the pathologic state, which is, as previously mentioned, an obstruction in an abdominal tube. Acute cholecystitis is merely a symptom of this underlying cause. It seems that this is the most commonly overlooked factor in the clinical evaluation of acute inflammation of the gallbladder.

Statistics show that a high mortality rate follows late drainage. This is true, but it is not fair to the surgical procedure of cholecystostomy, because it is so often chosen for patients who are too sick to withstand anything more serious and who would probably have died under any circumstances. Patients do not die as the result of drainage of the gallbladder; they die because it is deferred too long. These are procrastination deaths; they are not operative deaths. The very fact that cholecystostomy is the procedure of choice for the sickest patients indicates that drainage per se is the least serious and dangerous of all biliary operations. In this regard, the status of cholecystostomy is comparable to that of cesarian section of a few years ago in that they were both regarded more or less as "last resorts." The lowering of the mortality rate of cesarian section is undoubtedly due to early and preventive surgical intervention. If drainage of the gallbladder is used as a preventive procedure rather than as "the only thing to do because

the patient cannot stand anything else," it will lose its black name, and it will become an important factor in treatment too. Hence a brief and general discussion of the advantages of a two stage operation in certain cases of acute cholecystitis is presented. The first stage (drainage) is preventive for the immediately dangerous phase; the second stage is curative for cholecystopathy and the associated conditions.

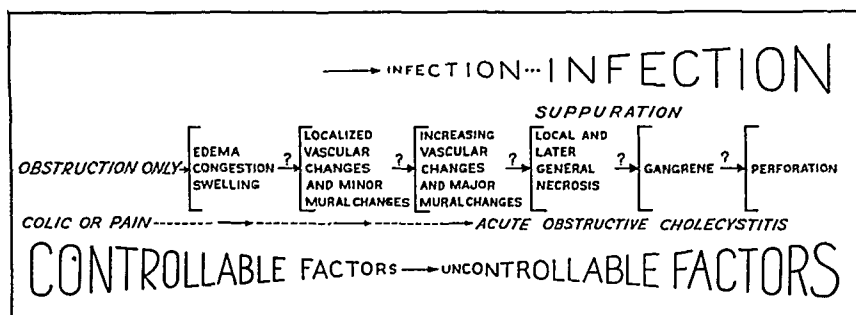
It would seem that a two stage operation answers many of the arguments of both the proponents and the opponents of immediate cholecystectomy. This procedure has greatly improved the surgical end results for other conditions, for example, certain types of perforative appendicitis, and for operations such as prostatectomy and many types of intestinal resection. It should therefore at least deserve serious consideration in this situation before being discarded, or even before being accepted. It is hoped that this presentation will stimulate such a discussion, which, however, cannot be thorough unless it is recognized that conservative (passive or medical) treatment does not control the factors which determine whether an acute obstruction of the cystic duct will resolve or progress to perforation. In conservative treatment the physician watches the course of acute obstructive cholecystitis but he does not change it. If it changes, it is changed by factors out of his control; that is, it resolves because of good luck and not because of good management, as witness the many instances in which it has occurred and subsided without the appearance of clinical signs or symptoms.

The suggestion is made, based on only 12 studied cases² and a thorough review of the literature, that the first stage, which is preventive and must be early, should consist of a simple and quick drainage of the bladder by use of a small mushroom catheter and when indicated a local anesthetic. This prevents the progression of pathologic changes to the dangerous phase and allows the physiologic functions to return to normal before extensive surgical procedures are performed. It obviates, moreover, what some authors refer to as the life-saving measures which should be resorted to before the so-called delayed operation is done, a warning which, in itself, means that the patient must present a bad risk for surgical intervention. Drainage allows the pressure inside the bladder to be reduced below the perforating point, if not to zero, in addition to preventing the immediately serious and potentially fatal complications. Drainage also predisposes to a quicker and more sure convalescence and reduces the incidence of pericholecystitis, of fistula formation and of other conditions, which make trauma a major factor in later surgical treatment. At the time of drainage an effort must, of course, be made to remove calculi from the cystic duct. This will consist in treating prophylactically and somewhat curatively the entire ductal system, particularly the common duct, by free drainage through the cystic duct, provided edema, swelling and congestion have not completely obstructed the latter; if such inflammatory obstruction is present, the removal of the mechanical obstruction and/or the release of the intravesical pressure would promote resolution in the area of the cystic duct and allow drainage from the great ducts. If drainage is performed early, few adhesions will be broken; local peritonitis will not likely be extended; the immediate dangers will, for practical purposes, be abolished, and cholecystectomy plus the often necessary operation on the ducts, which constitutes the second stage, will be done in a patient who presents a better risk owing to the absence of an acute pathologic condition and unbalanced physiologic processes. Thus the immediate and dangerous phase is passed over with a minimum of danger as interpreted by the

2. Seven personally observed cases and 5 studied by permission of Drs. A. H. Greenwood, A. M. Anderson, J. S. Sheahan, A. D. Konkin and W. D. Cornwall.

internist as well as by both the radical and the conservative surgeon. This procedure is physiologically and pathologically sound. It is also conservative therapy, and it is based on the often proved and well recognized surgical axiom that the progression or regression of any pathologic process which is the result of complete obstruction of a tube depends directly and indirectly on the release of that obstruction. This principle applies to any hollow viscus, whether it is the cystic duct, the small bowel (strangulated hernia) or a blood vessel (embolism). Rational treatment for any patient with abdominal obstruction is the release of that obstruction. And yet the physician often "sits by the patient" with acute obstruction of the cystic duct! This is often physiologically and pathologically unsound, no matter how favorable the results of a "watching and waiting" regimen may seem. Conservative medical treatment is not successful just because the patient does not die.

There is general agreement that the therapy of chronic calculosis should never be expectant; and both the immediate and the future dangers of acute diseases are greater.³ It therefore follows that the treatment of acute disease should, theoretically, never be expectant. When a patient first complains of symptoms of obstruction of the bowel one does not wait for signs or symptoms to appear which prove that the obstruction is complete and progressing; one prevents as much "trouble" as possible by using surgical intervention judiciously and prophylactically. This is the spirit in which cholecystostomy should be employed.



This represents, in a schematic way, the principal steps in the possible progress of acute cholecystitis when it is treated conservatively. Early in its course, when the obstruction is uncomplicated, the controllable factors are maximal; as the calculus becomes locked in place and local changes occur, these controllable factors gradually decrease until when infection is added to the minor complications they completely disappear and become the uncontrollable factors, which increase in direct proportion to the progress of the infection. These uncontrollable factors include physiochemical imbalances, hepatic damage, infection and suppuration. Fortunately, these late complications are not too common (though they are not uncommon).

The second stage, which is the actual *curative* effort, allows cholecystectomy to be performed and the ductal system to be treated with much less risk, much less trauma and much more thoroughness. This two stage attack is of particular significance for the older age group.

There is also the added and obviously important advantage in the two stage operation of one's being able to view the intrahepatic and extrahepatic ductal system by cholangiography and to determine the location and size of calculi in the ducts, if any are there, before the second operation. Perfusion can also be performed in selected cases and may be of great value.⁴

3. One of these dangers concerns the sudden upset in the physiochemical balance of the liver, which in chronic disease has had an opportunity to become partially balanced. This is less likely to happen in acute cholecystitis, because there are two pathologic processes involved.

4. Macdonald, D., and Drysdale, H. R.: Surgical Treatment of Medical Jaundice, *Am. J. Surg.* 60:122 (April) 1943.

Those who prefer conservative therapy and argue that surgical intervention is easier and safer after the subsidence of acute symptoms will probably agree that the two stage operation has much in its favor because the potential complications consequent on conservative treatment are reduced to a minimum, because the dangers and difficulties of later cholecystectomy are minimized and because thorough and curative surgical procedures, particularly on the ductal system, are better performed at a later date. It will probably find less favor with those who believe in early radical operation.

A NOTE REGARDING OBSTRUCTIVE JAUNDICE

In selected cases a two stage operation for the relief of inflammatory obstructive jaundice, which is one of the most potentially serious of the common conditions with which the surgeon has to deal, has some of the advantages just mentioned, but there are added ones. (This obviously does not apply to obstructive lesions in the hepatic ducts.) This procedure is also of value if jaundice is the result of acute hepatitis consequent on acute cholecystitis. (By the two stage method the curative procedures, which are usually necessary and which are often technically difficult, are not performed on a patient who represents a bad risk.) Certain it is that cholecystostomy, performed with a local anesthetic, will not produce the morbidity or the mortality that results from extensive surgical interventions on jaundiced patients, because the physicochemical upset consequent on obstructive jaundice is great. The patient is also spared submission to anesthesia in his serious condition. It is recognized, of course, that the dangers are usually reduced if the bilirubin content of the blood is allowed to become stationary or preferably to return to normal, but during this stage of waiting the liver is continually being damaged, particularly if the time elapsed is long. The two stage attack will also permit the many advantages of cholangiography to be made use of.

COMMENT AND SUMMARY

The present criteria for determining the type and the timing of the treatment of acute cholecystitis do not seem to be pathologically sound. For instance, the time element is too variable; the type of operation is not constant; the influence of anesthesia is rarely mentioned; the individual constitutional stability of patients cannot be evaluated in large groups, and the condition is often considered as a disease entity whereas it is really a symptom and a sign of a serious abdominal condition, namely, an acute obstruction. The potential seriousness of all obstructive lesions is well recognized; they demand active and early treatment. There is also failure to consider this condition as positive evidence of progressing pathologic change of the biliary system and to remember that the clinical picture is not always correlated to the active pathologic process.

A two stage surgical procedure is suggested as a new method of treatment in certain cases, particularly when the lesion is in an early stage, and is based on the etiologic factors and the resultant pathologic state. The first stage consists of cholecystostomy, which is preventive, and the second stage of cholecystectomy plus a ductal operation, which is curative.

The two stage operation has lowered the mortality of many surgical conditions and operations, for example, of some types of perforative appendicitis and of many types of resection of the bowel. It is suggested that the same basic principles deserve serious consideration in connection with certain types of biliary disease.

Some advantages of a two stage operation for patients suffering with obstructive (inflammatory) jaundice are also mentioned.

The theoretic and practical advantages of the two stage procedure are summarized as follows and are presented with the hope that they will stimulate a thorough discussion and evaluation of this important subject.

(1) In cases of acute cholecystitis:

- (a) That it prevents the serious or the potentially fatal complications resultant on conservative treatment.
- (b) That it averts pericholecystic pathologic changes (e. g. fistula formation) which make trauma a serious factor at later operations and, indeed, may make curative surgery possible only in the hands of the most experienced.
- (c) That cholangiography may often be of great help before the second stage.
- (d) That cholecystectomy and surgical treatment of the common duct (which is so often a part of successful surgical treatment of the gallbladder) can be performed with much more thoroughness and safety in a quiescent stage than during the acute active phase.
- (e) That it obviates dangers related to removal during the acute stage, not the least of which is a traumatic stricture of the common duct.
- (f) That it predisposes to the return of a normal physiochemical balance and a general improvement in the physical status before extensive surgical intervention is done.

(2) In cases of obstructive jaundice:

- (a) That the serious and always potentially dangerous surgical work is performed on a patient who presents a much safer risk at the second stage, in the absence of jaundice and in the presence of improved biliary and hepatic function.
- (b) That cholangiography may be a definite help in the second stage, in that the presence and location of ductal stones can be determined.
- (c) That perfusion will have helped to improve the blood and lymph circulation and to remove infection throughout the biliary system.
- (d) That the decompression of the liver is much more gradual and less dangerous when carried out slowly through the gallbladder.
- (e) That the morale of the patient is improved tremendously after the first stage, when the jaundice is reduced and the symptoms subside. This cannot be stressed too much.

INFLUENCE OF HEPATIC FUNCTION ON METABOLISM OF VITAMIN A

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Many facts indicate an influence of the liver on the metabolism of vitamin A. In acute¹ and chronic² hepatic disease the vitamin A content of the blood is low. Night blindness due to deficiency of vitamin A has been reported in acute hepatitis³ and in cirrhosis even without jaundice.⁴ The vitamin A content of the liver is low in chronic hepatitides (cirrhoses)⁵ and variable in acute hepatitis and in catarrhal or arsphe~~x~~amine jaundice.⁶ The histologic distribution of vitamin A in the liver is considerably changed by damage to the liver.⁷ Several factors have been mentioned to explain the foregoing observations, such as: (1) faulty absorption of vitamin A and especially of carotene from the intestinal tract⁸; (2) inability of the liver to store vitamin A, although more emphasis is laid on alterations of the reticuloendothelial system than on damage to the hepatic parenchyma⁹; (3) inability of the liver to convert carotene into vitamin A¹⁰; (4) an increased demand for vitamin A in hepatic disease.¹¹ However, the mechanism of this disturbance is still not clear. Knowledge of the mechanism of the disturbance of the metabolism of vitamin A in hepatic disease is necessary for its correction.

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Studies of biopsy specimens from the liver¹² were undertaken to compare the level of vitamin A in the blood before and after feeding of large doses of vitamin A with the hepatic content of vitamin A and with its distribution as seen by fluorescence microscopy. In addition, routine and fluorescence microscopic study of a great number of biopsy specimens from the liver provided an opportunity to investigate the incidence of anatomic changes in the liver in the diseases studied, especially since the normal morphologic pattern of the vitamin A fluorescence is disturbed before alterations are seen on routine histologic examination.¹³ From these studies information was obtained which, with the established knowledge, may clarify the relation between impairment of hepatic function and metabolism of vitamin A and at the same time give the indications for vitamin A therapy in hepatic disease.

MATERIAL AND METHOD

In 75 cases, biopsy specimens were taken at operations for various diseases affecting the upper part of the abdomen. The vitamin A content of the plasma was determined during operation. In most of the cases, several determinations of plasma vitamin A were made prior to the operation. In some of them the variation of the level following the administration of 75,000 U. S. P. units of vitamin A¹⁴ was observed (discussed in a previous paper¹⁵), and in 7 cases the influence of daily feeding of 500,000 U. S. P. units of vitamin A for three to six days was studied. These procedures are responsible for the occasional differences between the plasma vitamin A level during operation which was used for comparison with the hepatic level (described in a previous publication^{12b}) and the preliminary vitamin A level which is reported in the tables to follow. Since in the cases in which 500,000 U. S. P. units of vitamin A was given the hepatic vitamin A concentration was influenced by the huge doses, the hepatic values in the tables are marked by an asterisk but omitted from table 7. For completeness, the blood levels obtained in cases of cirrhosis and hepatitis are included in table 7 to provide comparative data on patients most of whom did not come to operation. In all cases some of the following clinical tests of hepatic function were performed prior to operation:

1. Determination of nitrogen, total protein, albumin and globulin of the plasma.¹⁶
2. Determination of plasma prothrombin concentration (Quick's method).¹⁷
3. Determination of icterus index.
4. Determination of blood cholesterol and cholesterol esters.¹⁸
5. Determination of alkaline serum phosphatase.¹⁹
6. Oral hippuric acid test.²⁰
7. Oral galactose tolerance test.²¹
8. Cephalin-cholesterol flocculation test.²²
9. Quantitative determination of excretion of urobilinogen in the urine and feces.²³

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The vitamin A was determined in the plasma and the liver, partly according to Josephs' method²⁴ and partly according to Kimble's,²⁵ with the photoelectric colorimeter. The values obtained by both methods, which were slightly modified, checked. The methods used were described in detail in a previous publication.^{12b} The part of the liver specimen which was used for histologic examination was fixed in solution of formaldehyde U. S. P. (diluted 1:10). After two hours frozen sections were made. Some of these were examined under the fluorescence microscope for vitamin A fluorescence and fat.²⁶ Other sections stained with sudan III were examined in visible light. The rest of the specimen was embedded in paraffin and sections stained according to routine methods.

The vitamin A distribution under the fluorescence microscope in necropsy and biopsy specimens from subjects with various pathologic conditions has previously been described.²⁷ In the normal liver vitamin A fluorescence may be imparted to the Kupffer cells by lipid droplets, to the epithelial cells by small lipid droplets at their edge, by mitochondria, by lipofuscin, by a few scattered large fat droplets and by the cytoplasm, which has a rather dull, diffuse fluorescence. The normal pattern of the vitamin A fluorescence is easily disturbed. Hence minor alterations were found in nearly all specimens of liver obtained for biopsy or necropsy. In definite pathologic conditions these alterations were extremely evident. One or more of the following alterations of the uniform fluorescence picture may occur. Irregular distribution of vitamin A fluorescence may be seen without change in the morphologic appearance in visible light. This irregularity may or may not be related to the topography of the lobule. Sometimes irregular foci are found with fluorescence obviously different from that of the surrounding tissue. In some areas only the Kupffer cells, and in others only the liver cells, show fluorescence, and in still others, neither shows it. The fine lipid droplets may be missing or irregularly distributed throughout the cell or be free of vitamin A fluorescence. Larger fat droplets of various sizes and in various numbers may be present with diminished, variable or no fluorescence. The tables which follow record the total amount of vitamin A fluorescence and the degree of alteration. The latter may be considered as a visual manifestation of disturbed vitamin A metabolism and also as a morphologic index of impairment of hepatic function.

To simplify the tabulation of the routine histologic examination the following symbols (numerals and letters) are used in describing the changes of the hepatic parenchyma and of the periportal triads respectively.

Hepatic Parenchyma.

1. Irregularity in the size of the cells and of the nuclei, usually combined with irregular mitosis.

2. Separation of the Kupffer cells from the hepatic cell cords. This mobilization is usually combined with proliferation of the Kupffer cells and widening of the tissue spaces between the hepatic cell cords and the blood sinusoids. The toxic edema or serous hepatitis²⁸ is usually localized. Its significance is questionable.²⁹

3. Accumulation of large fat droplets recognizable in visible light.

4. Leukocytic infiltration in the interstitial spaces (usually localized).

5. Scattered small foci of necrosis characterized by breaking up of the hepatic cell cords, lack of nuclear staining and leukocytic infiltration.

6. Central necrosis, often seen in jaundice and associated with imbibition of bile pigment. The areas of necrosis may show all stages from simple lack of nuclear staining, with imbibition of bile pigment, to disappearance of the hepatic cells in a wide central area with collapse of the framework, proliferation of the connective tissue and dilatation of the sinusoids.

7. Interstitial hepatitis, characterized by intralobular connective tissue proliferation, leukocytic infiltration, and necrobiosis with regeneration of the epithelial hepatic cells.

The changes represented by the numerals 5, 6 and 7 were considered definite evidence of parenchymal damage.

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A. Lymphocytic infiltration of the periportal field varying from a few scattered lymphocytes (seen in practically all cases) to dense infiltrations which nearly simulate lymph follicles.

B. Leukocytic infiltration of the periportal field mostly associated with cholangiolitis.

C. Enlargement of the periportal field due to proliferation of connective tissue (fibrosis).

D. Proliferation of the small bile ducts.

RESULTS

The patients examined are grouped according to their disease.

Peptic Ulcer.—Of 22 patients with gastric or duodenal ulcers, none showed signs of impaired hepatic function, except that 3 patients with bleeding ulcers had pathologic cephalin-cholesterol flocculation. Two livers showed fatty changes. In only 1 liver were there definite pathologic changes in the parenchyma. Lymphocytic infiltration and fibrosis were common in the periportal fields of all livers. The disturbance of the vitamin A fluorescence pattern was notable in only 1 case. The total amount of fluorescence was normal (fig. 1). The hepatic vitamin A concentration was also relatively high, and the blood vitamin A levels were with a few exceptions within normal limits. No great discrepancy between the level of vitamin A in the blood and in the liver was encountered (table 1).

Carcinoma of the Stomach.—In this group there were 7 patients with carcinoma and 1 with tuberculosis of the stomach. Three showed clinical signs of impairment of liver function, but in only 1 of them (the tuberculous patient) were definite pathologic changes present in the liver. Much vitamin A fluorescence with only moderately disturbed distribution was seen. Only the 4 patients not receiving large doses of vitamin A were representative for this study, but even these showed rather high amounts of hepatic vitamin A, which contrasted often with a low level of vitamin A in the blood (table 2).

Disease of the Gallbladder Without Jaundice.—In this group of 17 patients only 2 had questionable clinical evidence of damage to the liver. On histologic examination 1 showed miliary necroses and fatty changes and 4 had fatty changes only. The alterations in the periportal fields were much more developed than in the previous groups. The disturbance of the vitamin A fluorescence was not more evident than in the other groups. One phenomenon, however, was rather common, namely the frequent appearance of fat droplets without vitamin A fluorescence (fig. 2). Chemically and histologically the total amount of vitamin A in the liver was within normal limits. The blood levels were also fairly normal (table 3).

Disease of the Gallbladder with Jaundice.—This group included 13 patients with various degrees of icterus. Of the 11 patients examined, 4 showed definite, 4 questionable and 3 no clinical evidence of impairment of hepatic function. Morphologic evidence of damage to hepatic cells did not parallel the results of clinical tests of hepatic function. Signs of damage to hepatic cells were found in 6 cases, the incidence being fairly parallel to the duration of the jaundice. In none had the jaundice existed less than four weeks, while in those without damage to the liver the icterus was never of more than five weeks' duration. Pathologic changes in the periportal field were common. The vitamin A fluorescence showed great variation in its total amount, and, especially in the patients with evidence of hepatic damage, the vitamin A fluorescence pattern was greatly disturbed (figs. 3 and 4). Even if the patients to whom large amounts of vitamin A were administered were omitted, the total amount of vitamin A in the liver varied between 7 and 140 micrograms per gram of liver. The plasma vitamin A also showed great variation and was especially low in most of the patients with pathologic changes (table 4).

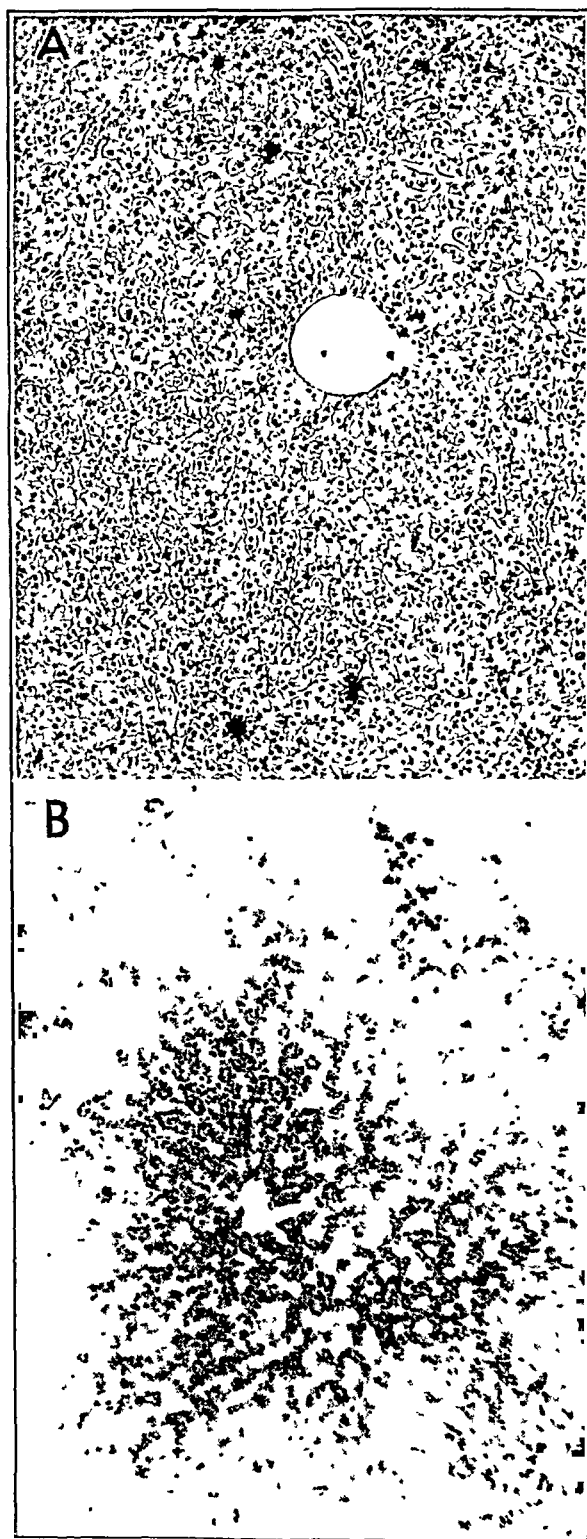


Fig. 1—Photomicrographs of a biopsy specimen from the liver of a patient with peptic ulcer without damage to the liver. *A*, routine histologic examination: normal structure of the hepatic parenchyma. *B*, examination with fluorescence microscope: vitamin A fluorescence imparted by fine lipid droplets at the edge of the liver cells and in the Kupffer cells.

TABLE 1.—Patients with Peptic Ulcer

Initials	Sex and Age	Site of Ulcer	Clinical Evidence of Damage to Liver	Routine Histologic Evidence of Damage to Liver		Fluorescence-Microscopic Observations		Vitamin A in Micrograms per 100 Cc. of Plasma	
				Paren-chyma	Periportal Field	Total Vitamin A Fluorescence	Degree of Disturbance of Distribution	Gm. of Liver	Vitamin A in Micrograms per 100 Cc. of Plasma
J. M.	F 54	Gastric.....	—	0	A	++	+	298	44
C. S.	M 63	Duodenal.....	—	3	A, C	++	++	124	28
A. K.	M 32	Duodenal.....	—	0	0	+	±	70	44
S. S.	M 49	Duodenal.....	—	0	A	++	++	29	35
F. D.	M 36	Duodenal.....	—	0	C	++	+	99	35
L. I.	M 56	Duodenal.....	—	0	A	++	+	113	53
W. N.	M 50	Gastric.....	—	0	A	++	+	49	25
W. M.	M 34	Duodenal.....	—	0	A	++	++	108	100
J. K.	M 45	Duodenal.....	—	0	A	++	+	59	16
F. D.	M 66	Gastric.....	—	4, 5	C	++	++	52	27
W. W.	M 42	Duodenal.....	0	0	A	++	++	63	33
R. M.	M 29	Duodenal.....	—	0	A	++	++	25	25
P. S.	M 59	Duodenal.....	—	1, 4	A	++	+	24	22
A. M.	M 67	Duodenal.....	—	2	A	++	+	99	33
Z. K.	M 23	Duodenal.....	0	0	A	++	++	167	22
J. N.	M 38	Duodenal.....	—	3	A, C	++	±	92	11
J. Z.	M 54	Duodenal.....	—	2	A	++	++	98	33
F. J.	M 52	Duodenal.....	—	0	A	++	++	47	43
F. T.	M 29	Gastric.....	?	0	A	++	+	56	11
E. S.	M 41	Duodenal.....	?	1	A	++	++	35	27
W. D.	M 34	Duodenal.....	?	1	A	++	++	93	22
R. G.	M 36	Duodenal.....	?	0	A	++	++	65	33
A. L.	M 40	Duodenal.....	?	1	A	++	++	37	11

TABLE 2.—Patients with Carcinoma of the Stomach

Initials	Sex and Age	Diagnosis	Clinical Evidence of Damage to Liver	Routine Histologic Evidence of Damage to Liver		Fluorescence-Microscopic Observations		Vitamin A in Micrograms per 100 Cc. of Plasma	
				Paren-chyma	Periportal Field	Total Vitamin A Fluorescence	Degree of Disturbance of Distribution	Gm. of Liver	Vitamin A in Micrograms per 100 Cc. of Plasma
J. S.*	M 57	Carcinoma of stomach.....	0	0	A	+++	±	123	10
J. H.*	M 33	Tuberculosis of stomach.....	?	2, 5	0	+++	++	307	24
L. O.*	M 28	Carcinoma of stomach.....	0	0	A	+++	++	435	17
G. B.*	M 56	Carcinoma of stomach.....	0	0	A	+++	++	548	44
N. C.	M 64	Carcinoma of stomach.....	0	0	A	+++	++	262	35
A. M.	F 69	Carcinoma of stomach.....	?	0	A	+++	++	429	22
J. P.	M 58	Carcinoma of stomach.....	?	2	A, D	++	++	31	11
H. G.	M 66	Carcinoma of stomach.....	0	2	0	+++	+	233	17

* Received several doses of 500,000 U. S. P. units of vitamin A.

Malignant Tumors with Jaundice.—In this group there were 10 patients, 1 of them examined twice, on occasion of two laparotomies. With the exception of 1 patient with only slight jaundice, all showed on clinical examination definite or questionable impairment of hepatic function and also showed pathologic changes in the hepatic parenchyma and the periportal fields. The total amount of vitamin A

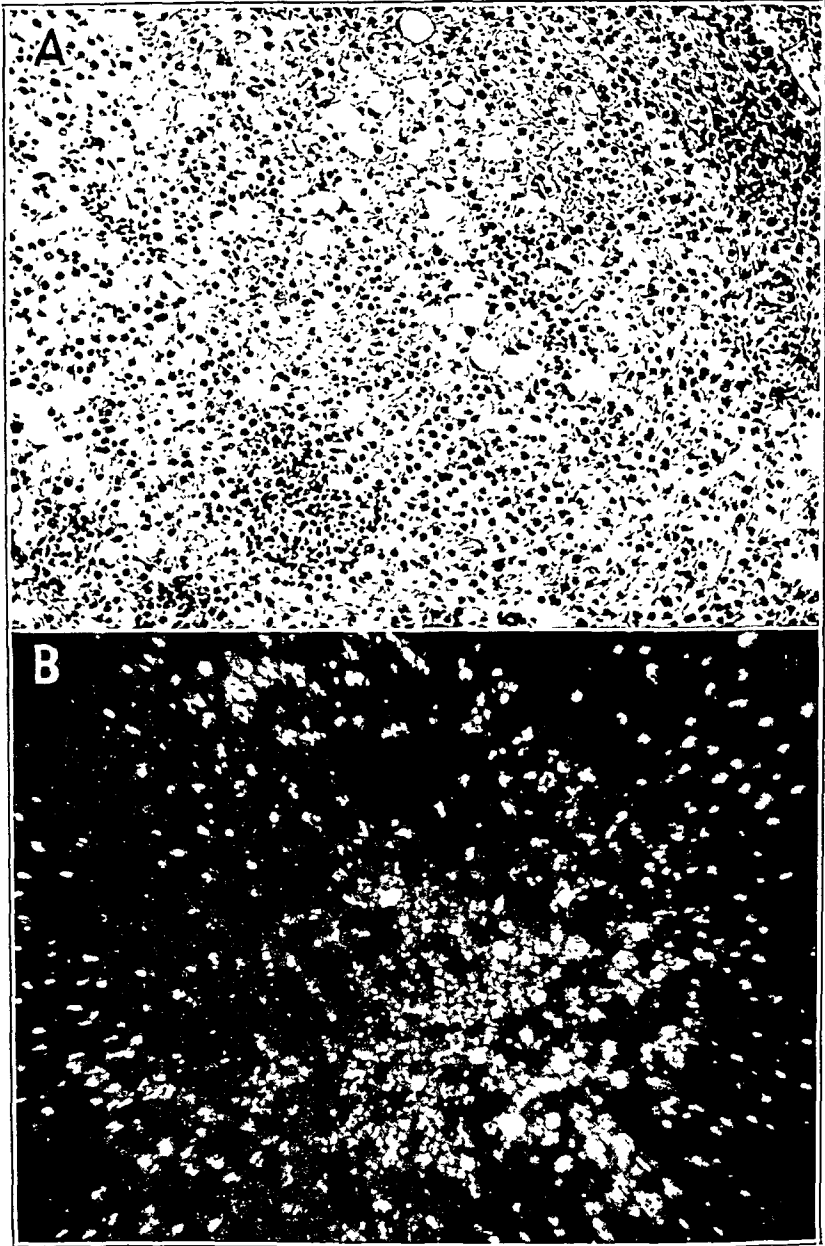


Fig. 2.—Photomicrographs of a biopsy specimen from the liver of a patient with gall-bladder disease without jaundice. *A*, routine histologic examination: many large fat droplets scattered over the hepatic parenchyma. Extensive lymphocytic infiltration in the periportal field. *B*, examination with fluorescence microscope: the Kupffer cells impart a strong vitamin A fluorescence. In places, small lipid droplets in the hepatic cells impart a strong fluorescence. The large fat droplets have a varying, but usually low, fluorescence.

fluorescence was as a whole lower in this group than in the others. The disturbance of the vitamin A fluorescence pattern was considerable (fig. 5). The concentration

TABLE 3.—Patients with Disease of the Gallbladder Without Jaundice

Initials	Sex and Age	Clinical Evidence of Damage to Liver	Routine Histologic Evidence of Damage to Liver		Fluorescence-Microscopic Observations		Vitamin A In Micrograms per 100 Cc. of Plasma	
			Paren- chyma	Periportal Field	Total Vitamin A Fluorescence	Degree of Disturbance of Distribution	Gm. of Liver	Gm. of Plasma
M. K.	F 56	0	1	A, O	++	++	31	27
A. F.	F 62	?	1	A	+++	+	106	61
P. M.	F 51	0	0	0	++	±	49	35
T. H.	M 48	0	1	A, B	++	++	41	20
C. F.	F 65	0	0	A	++	++	50	52
Z. I.	F 37	0	0	A	±	++	5	22
O. J.	F 41	0	0	O	+++	+	233	33
A. R.	F 29	—	0	A	++	+	41	27
L. M.	F 39	—	1, 4	A, C, D	+	++	35	33
L. B.	F 56	—	0	A	+++	+	217	38
A. P.	F 58	—	0	A	++	±	70	35
M. S.	F 52	—	3	A	++	+	74	66
U. L.	F 31	—	3	A	+++	+	62	33
M. F.	F 53	?	3, 5	A, C	+++	+	88	38
C. W.	F 46	0	3	A, C	++	++	20	33
L. B.	F 31	—	0	A, C	++	+	60	38
L. G.	F 36	—	3	A	+++	++	41	27

TABLE 4.—Patients with Disease of the Gallbladder with Jaundice

Initials	Sex and Age	Icterus Index	Duration of Jaundice	Clinical Evidence of Damage to Liver	Routine Histologic Evidence of Damage to Liver		Fluorescence-Microscopic Observations		Vitamin A In Micrograms per 100 Cc. of Plasma	
					Paren- chyma	Periportal Field	Total Vitamin A Fluorescence	Degree of Disturbance of Distribution	Gm. of Liver	Gm. of Plasma
J. D.*	M 62	15	6 weeks	0	2, 4, 7	A	+++	++	205	44
J. N.	F 46	43	1 year	+	1, 7	C	+	++	80	3.5
F. T.	M 55	150	15 days	0	1	A	++	++	130	2
J. K.	M 23	37	10 weeks	+	4, 6	A, B, D	±	++	50	0
R. B.	M 69	75	3 weeks	?	5	A	++	++	11	6
F. S.	F 44	53	8 weeks	0	1, 5	A, C, D	±	++	40	27
F. A.	M 52	111	4 weeks	?	0	A, C	++	++	7	4
M. M.	F 57	25	5 weeks	?	0	A	+++	++	140	17
I. H.	F 15	25	2 weeks	+	0	A	+++	++	122	33
A. M.	F 42	16	2 weeks	—	3	A	+	++	37	31
F. S.	F 31	46	1 week	—	3	a, c	+++	++	15	38
M. B.*	F 69	24	3 weeks	?	1	A	+++	±	383	27
A. M.	F 22	58	2 weeks	+	0	A	++	+	81	22

* Received several doses of 500,000 U. S. P. units of vitamin A.

of vitamin A in the plasma and in the liver was relatively low, although the decrease in the plasma was often much more marked than that in the liver, producing evident discrepancies between the amount of vitamin A in the plasma and in the liver (table 5).

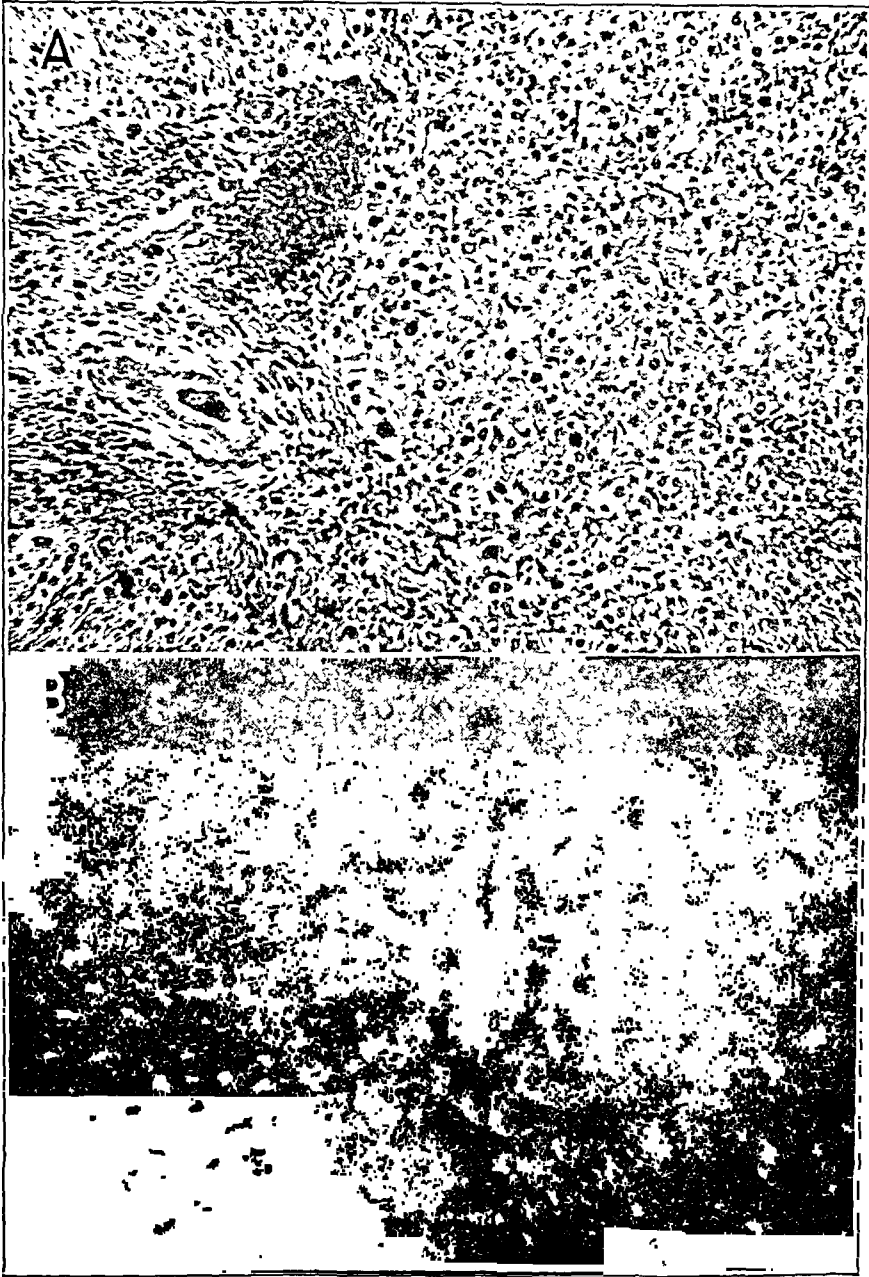


Fig. 3.—Photomicrographs of a biopsy specimen from the liver of a patient with disease of the gallbladder with jaundice of short duration and without clinical signs of damage to the liver. *A*, routine histologic examination: extensive lymphocytic infiltration in the enlarged periportal field. No visible damage to the parenchyma. *B*, examination with fluorescence microscope: irregular vitamin A fluorescence is imparted almost only by Kupfer cells. The bile casts in the enlarged bile capillaries appear black.

Cirrhosis.—Five patients with cirrhosis were examined. One had Wilson's disease (fig. 6); 1 had cirrhosis with primary carcinoma, and 3 had periportal

cirrhotoses (fig. 7). The first 2 had no clinical evidence of damage to the liver, while the last 3 had such evidence and showed anatomic changes on histologic examination. In the latter 3 patients the plasma levels were zero, and in 2 of them

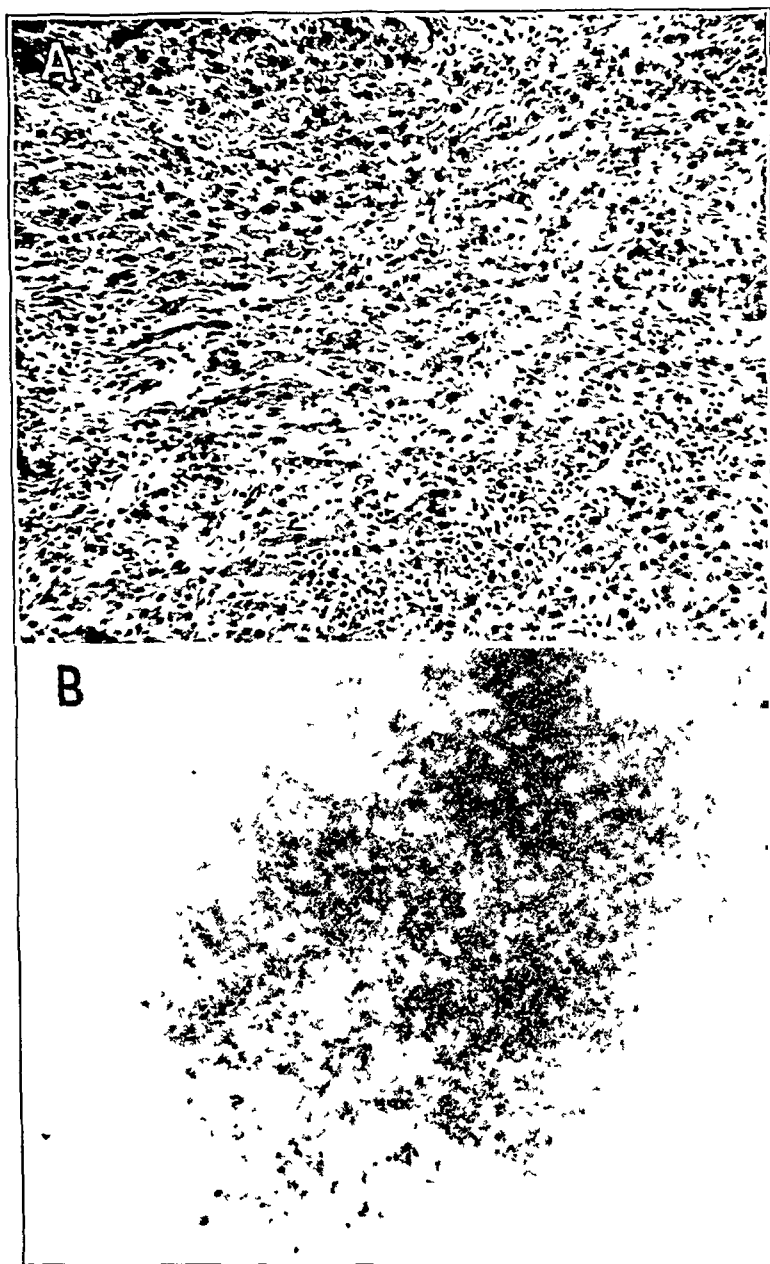


Fig. 4.—Photomicrographs of a biopsy specimen from the liver of a patient with disease of the gallbladder with jaundice of one year's duration and with clinical signs of hepatic damage. *A*, routine histologic examination—interstitial proliferation of connective tissue. Leukocytic and lymphocytic infiltration. *B*, examination with fluorescence microscope—small amounts of vitamin A fluorescence are seen in highly irregular distribution in Kupfer and hepatic cells.

the hepatic concentration was low. The distribution of the vitamin A fluorescence was much disturbed (table 6).

TABLE 5—*Patients with Cancer of the Biliary Tract*

Initials	Age and Sex	Site of Lesion	Icterus Index	Duration of Jaundice	Clinical Evidence of Damage to Liver	Routine Histologic Evidence of Damage to Liver		Fluorescence Microscopic Observations		Vitamin A in Micrograms per 100 Cc of Plasma	
						Parenchyma	Periportal Field	Total Vitamin A Fluorescence	Degree of Disturbance of Distribution	Gm of Liver	
M R	M 52	Pancreas	333	2 weeks	+	2, 6	B, C, D	++	+++	110	0
A D	F 63	Stomach	103	3 weeks	+	1, 2, 6	A	+	+++	21	6
F F	M 14	Pancreas	156	8 months	+	6	A, B	+	+++	20	0
P M	M 29	Retropertoneal sarcoma	150	5 months	+	6	A, B, C	—	—	40	22
M B	M 34	Pancreas	225	6 months	?	Biliary cholangitic cirrhosis		±	+++	5	5
W M*	M 60	Ampulla of Vater	56	5 weeks	+	1	A, B	++	+++	127	0
W M	M 60	Ampulla of Vater	50	7 weeks	+	1, 4	A, B	++	+	86	25
M E	F 67	Retropertoneal tumor	8	?	0	0	A, C, D	++	+	187	17
D S	M 75	Pancreas	312	5 weeks	?	4, 6	A, B, C	±	++	32	0
E D	F 69	Pancreas	71	8 weeks	+	1, 4, 5	A, C	+	++	55	6
M K	F 56	Pancreas	47	1 week	+	1, 6	A, O	+	+++	63	15

*Received several doses of 500 000 U S P units of vitamin A

TABLE 6—*Patients with Cirrhosis of the Liver*

Initials	Sex and Age	Diagnosis	Icterus Index	Clinical Evidence of Damage to Liver	Routine Histologic Evidence of Damage to Liver		Fluorescence Microscopic Observations		Vitamin A in Micrograms per 100 Cc of Plasma	
					Parenchyma	Periportal Field	Total Vitamin A Fluorescence	Degree of Disturbance of Distribution	Gm of Liver	
I H	M 24	Wilson's disease	6	0	0	A, C, D	++	+	83	35
E T	M 60	Cirrhosis and carcinoma of liver	7	0	Tumor tissue		±	+++	11	8
F G	M 39	Cirrhosis	10	+	Extensive decompensated cirrhosis		±	+++	0.2	0
J M	M 54	Cirrhosis	150	+	1	A, C, D	±	+++	3.5	0
H B	M 61	Cirrhosis	100	+	1.6	A, B, C, D	+	+++	7.4	0

TABULATION OF ALL THE FACTS OBTAINED

From table 7 it is evident that zero levels of vitamin A in the plasma were found in this series only in patients with far advanced damage to the liver. All the patients with cirrhosis with jaundice and 66 per cent of those with primary or

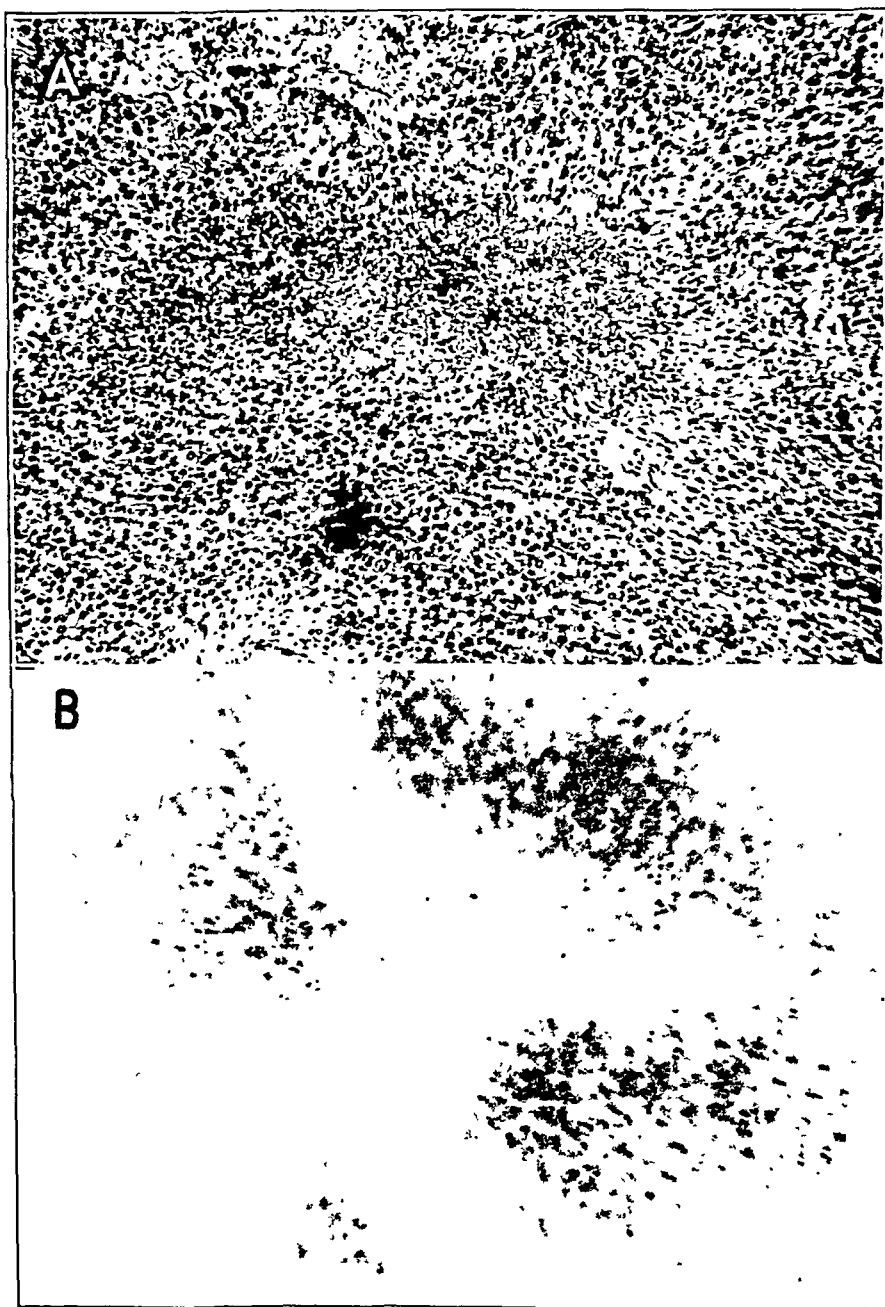


Fig. 5.—Photomicrographs of a biopsy specimen from the liver of a patient with jaundice due to malignant obstruction and with clinical signs of damage to the liver. *A*, routine histologic examination: central biliary necrosis with leukocytic infiltration. The surrounding hepatic parenchyma of the intermediary zone appears normal. *B*, examination with fluorescence microscope: the area of central biliary necrosis is free of vitamin A fluorescence. The bile casts appear as black spots. In the surrounding hepatic parenchyma irregular vitamin A fluorescence is imparted by the Kupffer cells and by some lipid droplets in the hepatic cells.

secondary hepatitis due to obstructive jaundice from carcinoma of the biliary tract had zero levels of vitamin A in the plasma. Some instances of a zero level were also found in patients with cirrhosis without jaundice or with secondary hepatitis from prolonged incomplete obstructive jaundice due to cholelithiasis. Paralleling

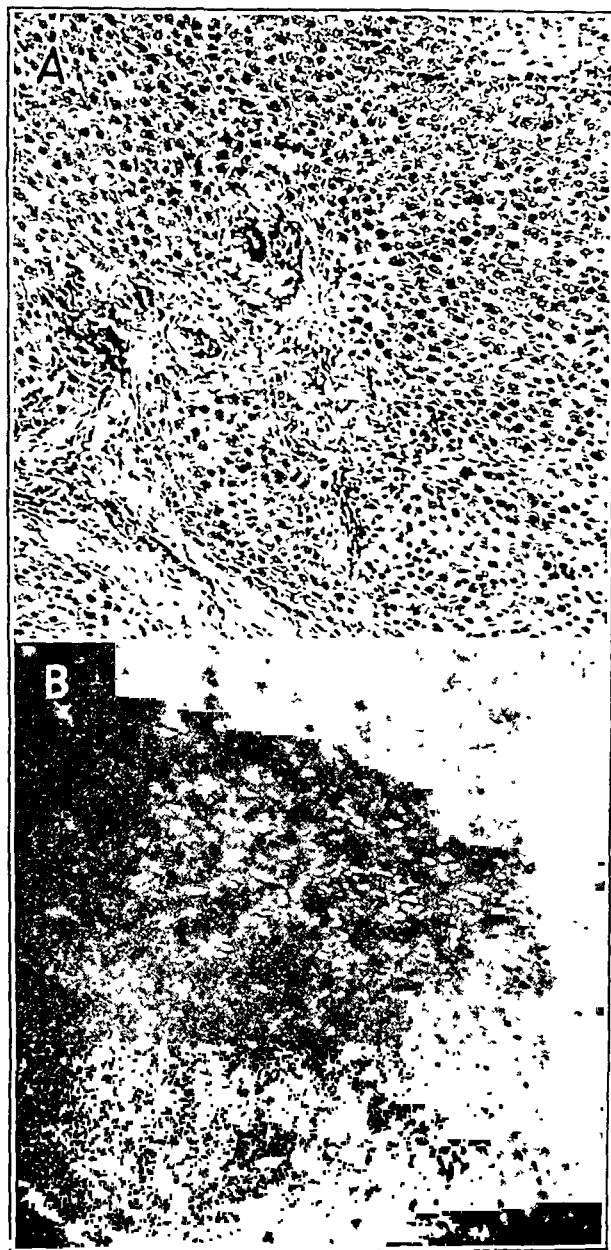


Fig. 6.—Photomicrographs of a biopsy specimen from the liver of a patient with compensated cirrhosis (Wilson's disease). *A*, routine histologic examination: enlargement of the periportal field due to fibrosis and lymphocytic infiltration. Proliferation in bile ducts—no signs of damage in the hepatic parenchyma. *B*, examination with fluorescence microscope: irregular distribution of the vitamin A fluorescence which is imparted by bizarre-shaped Kupffer cells and and irregularly distributed lipid droplets in the hepatic cells.

the incidence of zero levels the average of the plasma vitamin A levels in the aforementioned groups is very low. In benign or malignant obstruction there is a definite difference in the average of the plasma levels between the patients with

and those without hepatitis. Of the 3 patients in the other groups with morphologically apparent damage to the liver, only 1 had a low level of vitamin A in the plasma. The presence of extensive fatty changes, especially frequent in cholelithiasis, did not influence the levels of vitamin A in the plasma.

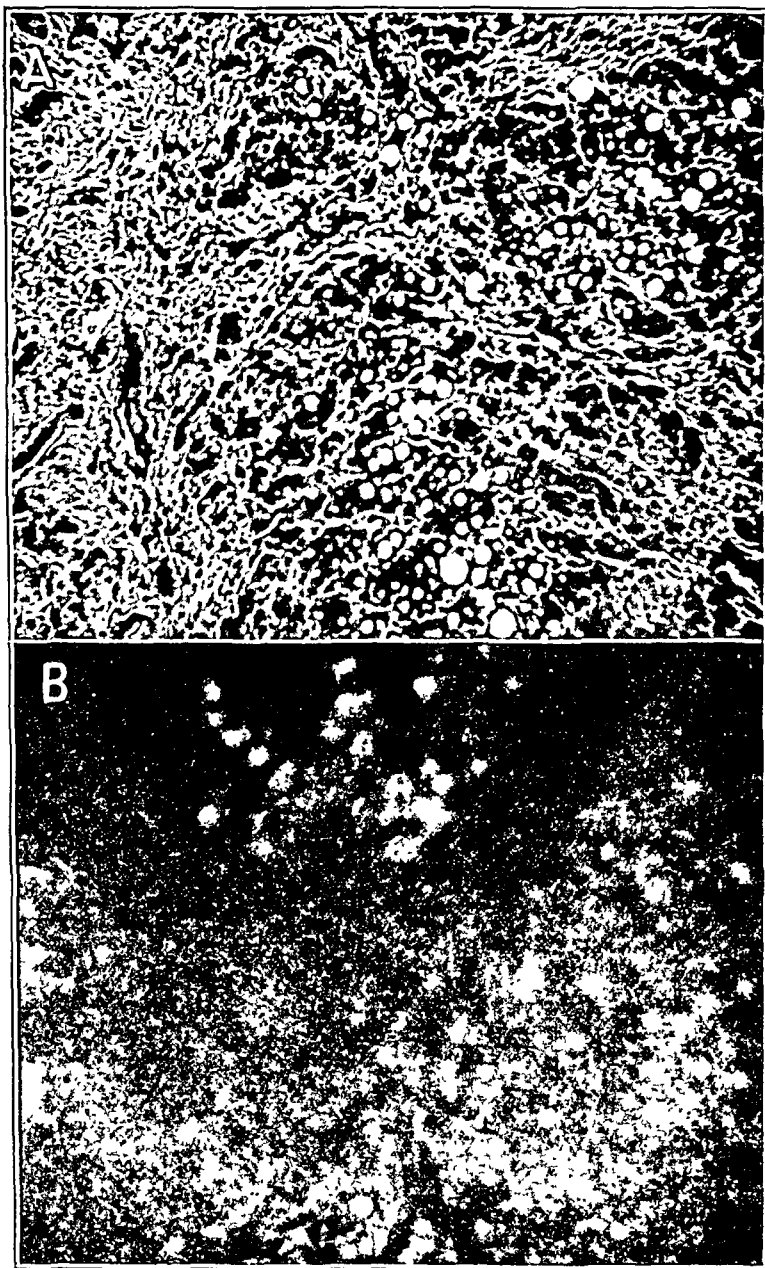


Fig. 7.—Photomicrographs of a biopsy specimen from the liver of a patient with cirrhosis with jaundice. *A*, routine histologic examination: extensive proliferation of connective tissue with lymphocytic infiltration and proliferation in the bile ducts. Many fat droplets of various sizes in the hepatic parenchyma. The cytoplasm of the hepatic cells is dark. *B*, examination with fluorescence microscope: vitamin A fluorescence imparted by a few irregularly shaped Kupffer cells and by the large fat droplets, the fluorescence of which is very low.

The average hepatic levels showed similar tendencies. They were low in the cases with damage to the liver and jaundice. Again, there is the characteristic

difference between cirrhosis with and without jaundice and benign and malignant obstruction with and without secondary hepatitis. Generally, the variations in the concentration of vitamin A were not as great in the liver as in the plasma, thus producing often a great discrepancy between a low content in the blood and a relatively high content in the liver. For comparison with the hepatic content of vitamin A the plasma obtained during operation was used. Its vitamin A level was often different from that of the first specimen, owing to preoperative administration of vitamin A. The discrepancy between the concentration in the liver and that in the plasma was especially evident in carcinoma of the stomach, although there was no morphologic evidence of damage to the liver. Absence of an increase in plasma vitamin A following administration of vitamin A was most common with damage to the liver.

COMMENT

The results of this study open two avenues of thought: (1) the relation of the disturbance of the liver to the metabolism of vitamin A and the therapeutic

TABLE 7.—*Summary of Data on Seventy-Seven Patients Subjected to Operation and Thirty Patients with Hepatic Disease Who Were Not Operated On*

Diagnosis	Total Num- ber of Patients	Number of Patients with Plasma Vitamin A Level of	Average Concentra- tion of Vitamin A, in Micrograms per 100 Cc. of Plasma		Average Concentra- tion of Vitamin A in Micro- grams per Gram of Liver
			Prelimi- nary	During Opera- tion	
Cirrhosis without jaundice.....	10*	1	13	17	54
Cirrhosis with jaundice.....	16†	13	1	1.8	21
Hepatitis.....	9‡	5	3	—	—
Carcinoma of biliary passages with secondary hepatitis.....	10	6	7	8§	53§
Carcinoma of biliary passages without secondary hepatitis...	1	0	17	17	187
Disease of gallbladder without jaundice and with hepatitis.....	6	1	14	11§	33§
Disease of gallbladder without hepatitis.....	7	0	24	31§	97§
Disease of gallbladder without jaundice and without hepatitis	11	0	34	35	67
Disease of gallbladder without jaundice and with hepatitis....	1	0	39	39	88
Disease of gallbladder with fat in liver.....	5	0	39	39	83
Carcinoma of stomach without damage to liver.....	7	0	24	21	238
Tuberculosis of stomach with damage to liver.....	1	0	2.3	—§	—§
Peptic ulcer without damage to liver.....	22	0	35	33	92
Peptic ulcer with damage to liver.....	1	0	27	27	63

* Eight of these were not operated on.

† Thirteen of these were not operated on.

‡ None of these were operated on.

§ One patient left out because he received 500,000 U. S. P. units of vitamin A.

|| Three patients left out because they received 500,000 U. S. P. units of vitamin A.

considerations derived from it, and (2) the utilization of chemical and of fluorescence-microscopic demonstration of vitamin A in ascertaining the presence and degree of damage to the liver.

Confirming previous reports, this study also reveals that with damage to the liver the level of vitamin A in the plasma is low. The lowest averages and the most zero levels (with the method used) are found in progressive cirrhosis with superimposed hepatitis and manifest jaundice. In cirrhosis without acute hepatitis as indicated by the absence of manifest jaundice the average plasma vitamin A level is slightly higher. Similarly, with obstructive jaundice the lowest levels are found in patients with superimposed hepatitis, in agreement with Stewart and Rourke.³⁰ In our cases the secondary hepatitis was more common in cancerous complete biliary obstruction than in benign incomplete obstruction. With uncomplicated obstructive jaundice the level of vitamin A in the plasma is almost normal.

In the absence of gross nutritional deficiency, a plasma vitamin A level of zero indicates severe damage to the liver whether jaundice is present or not or whether the hepatitis is primary or secondary to an obstructive phenomenon. In the 3

patients without obvious hepatic disease or jaundice in whom the histologic examination revealed miliary necrosis of the hepatic parenchyma, the plasma level was low in only 1. However, the functional significance of the necrosis is questionable, as will be discussed later. A normal blood level of vitamin A does not necessarily exclude some damage to the liver; a zero or close to zero level is definite evidence of damage to the liver provided nutritional factors can be excluded. Lack of vitamin A in the blood may even be of diagnostic value comparable to that of the known drop of vitamin K activity in similar conditions. Confirming the observations of Abels and his associates³¹ in cases of carcinoma of the stomach, somewhat low plasma vitamin A levels were found which were associated with normal hepatic stores of the vitamin and relatively high incidence of functional impairment of the liver. An explanation for this cannot be given at present.

To explain the low plasma level of vitamin A in hepatic disease and its significance from the point of view of vitamin A therapy, prior studies on the relation between plasma and liver vitamin A^{12b} and the intestinal absorption of vitamin A can be referred to.¹⁵ In patients with a low plasma level of vitamin A and damage to the liver, we found, as did others,³² an impaired intestinal absorption of vitamin A; the blood level failed to rise on oral administration of 75,000 U. S. P. units of vitamin A. The nearest explanation for the disturbed absorption of vitamin A would be the jaundice, since lack of bile acids prevents the absorption of carotene¹⁰ and possibly interferes with that of the fat-soluble vitamin A. The impairment of absorption, however, does not run parallel to the degree and type of jaundice—hepatic or obstructive. Low blood levels of the vitamin are also found in cirrhosis without jaundice. Hence the hepatic damage itself is probably responsible. However, impaired absorption is not the only factor causing a lack of vitamin A in the plasma. In acute hepatitis the impairment of absorption does not exist long enough to deplete the blood if the stores in the body are sufficient. A diet completely free of vitamin A fails for a long time to reduce the plasma vitamin A in normal adults.³³ The relation between the vitamin A content of the liver (which contains 95 per cent of the vitamin A in the body³⁴) and that of the plasma is significant. If, as seen under the fluorescence microscope, the distribution of vitamin A in the liver becomes too much altered, the regulation of the blood level by the release of vitamin A from the liver is disturbed. Two factors, therefore, explain the low levels in hepatitis: impairment of intestinal absorption and inability of the liver to release vitamin A. These may be enhanced by insufficient vitamin A intake, especially since carotene is probably not utilized.

Is the low blood level of vitamin A in disease of the liver an indication for treatment with vitamin A? The hepatic concentration of vitamin A cannot determine vitamin A therapy, since vitamin A in the liver is not always available for release. The blood levels, therefore, indicate the vitamin A status and the necessity for treatment. The lack of functional vitamin A is proved by the night blindness associated with acute hepatitis when the liver depots are still normal. The rationale of vitamin A treatment for disease of the liver is evident from

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investigation on rats with experimental damage to the liver produced by carbon tetrachloride or some other poison.³⁵ In the livers of such rats, vitamin A accumulates in pathologic fat depots and disappears from the normal sites in the morphologically unchanged parenchyma. If moderate amounts of vitamin A are fed to vitamin A-deficient rats intoxicated with carbon tetrachloride, it is primarily taken up by the pathologic fat deposits in the liver. This vitamin A is less readily utilized. Only the feeding of large amounts of vitamin A produces storage in the normal sites also. When the human liver is damaged and vitamin A is stored in pathologic sites from which it is less readily utilized, it is thus desirable to administer extremely large doses of vitamin A. These will first saturate the pathologic areas, with their higher affinity, and then impregnate the normal sites. In addition, such large doses compensate for the disturbed intestinal absorption. That such large doses actually increase the amount of vitamin A in the liver and in the blood has been shown by our feeding experiments with 500,000 U. S. P. units of vitamin A and by those of others.³⁰ Our present experiences, however, do not allow us to state exactly the quantity indicated when the liver is damaged.

The morphologic demonstration of impairment of hepatic function is still in an unsatisfactory state, not far ahead of clinical tests of hepatic function. The morphologic demonstration of central necrosis with or without imbibition of bile or dispersed miliary necrosis proves that just a small amount of hepatic parenchyma has been put out of function. Since only a fifth of the hepatic parenchyma is sufficient to carry out the function of the liver, the opinion that these small necrotic areas indicate general hepatic damage assumes without evidence that the histologically intact liver is also damaged. Generalized disturbance of the structure of the liver, like the diffuse toxic edema³⁰ or dissociation of the hepatic cell cords, is found in patients with or without disease of the liver. The only definite signs of diffuse damage to the liver seen in routine histologic study are diffuse interstitial hepatitis and diffuse necrosis of hepatic cells, as in acute yellow atrophy. If exact cytologic studies are omitted—as they usually are—no morphologic evidence for diffuse damage to the liver can be offered and hence the difficulty in correlating clinical tests with the results of routine histologic examination. Whether the 3 patients previously alluded to in whom localized areas of necrosis were not associated with impaired hepatic function actually had damaged livers is questionable. A generalized rather than focal disturbance of the characteristic pattern of the vitamin A fluorescence is more outspoken than the hard to evaluate changes in visible light. That it is a better index of functional impairment is not proved but seems probable.

In none of the specimens obtained at operation was the distribution of vitamin A as even and regular as in healthy, well fed and quickly killed animals (rats and dogs³⁶). Only in a few of the biopsy specimens (characterized by \pm) and in some postmortem specimens did the distribution approach the normal. In all others, various degrees of irregularity were present. According to this criterion, the liver was not completely normal in any patient coming to operation. Some aberrations from the norm in the periportal field were found in practically all cases, indicating some past or present injury. All evidence (clinical, routine histologic and fluorescence microscopic) points to definite parenchymatous damage in cirrhosis. Damage to the parenchyma of the liver is also very common with cancer of the biliary passages, where prolonged complete obstruction and/or

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36. Popper, H., and Greenberg, R.: *Visualization of Vitamin A in Rat Organs by Fluorescence Microscopy*, *Arch. Path.* **32**:11 (July) 1941.

infection are obviously responsible. In our series it was also quite common with cholelithiasis with biliary obstruction. The experience that severe damage to the liver will appear after prolonged biliary obstruction is thus confirmed. Our data would indicate four weeks as the limit before severe hepatic changes occur. Operation for cholelithiasis with jaundice is hence indicated before the end of this period. With ulcers and carcinoma of the stomach, hepatic damage of only slight degree is encountered.

Our cases of disease of the gallbladder contribute to the old controversy as to whether damage to the liver is present in uncomplicated cholelithiasis.³⁷ In our material the hepatic fatty changes were more common in the patients with this disease than in the other groups. Whether these fatty deposits without vitamin A fluorescence indicate a choline deficiency, as the fluorescence microscopic picture may suggest,³⁸ can be proved only by the results of choline therapy. Otherwise the incidence of damage to the hepatic parenchyma is only slightly higher than in the other nonjaundiced patients. Only the changes in the periportal field are somewhat more prominent. Investigations are under way to correct the described limited disturbances of the hepatic parenchyma.

CONCLUSIONS

The concentration of vitamin A in the plasma and in the liver (biopsy specimens) and its fluorescence microscopic distribution in the liver have been compared with the results of tests of hepatic function and the routine histologic picture of the specimens.

The plasma level of vitamin A is low when the liver is damaged and is slightly lowered in carcinoma of the stomach. If gross nutritional deficiency can be excluded, a plasma vitamin A level of zero points to severe damage to the liver. In cirrhosis with jaundice and in obstructive jaundice with hepatic damage, the plasma level is lower and the incidence of zero levels higher than in cirrhosis without jaundice and obstructive jaundice without hepatic damage, respectively.

The hepatic vitamin A concentration is often, but not always, reduced when the liver is damaged.

The fluorescence-microscopic pattern of vitamin A distribution is never completely regular. Severe irregularities, however, were found only in cases of hepatitis, cirrhosis or obstructive jaundice with secondary hepatitis. The milder degrees of disturbances of the microscopic picture are considered to indicate slight hepatic damage, not recognized by means of routine histologic examination.

The low blood level of vitamin A in hepatitis is a sign of functional deficiency of the vitamin explained by impairment of (a) the release of vitamin A by the liver and (b) the absorption of vitamin A from the intestinal tract.

The rationale of administration of large doses of vitamin A in cases of hepatic disease is to overcome the impaired intestinal absorption and to saturate the pathologic fat deposits in the liver in order to impregnate the normal site.

Fluorescence-microscopic changes in the distribution of vitamin A and changes in the periportal field point to functional impairment of the liver in practically all patients coming to operation because of disease of the upper part of the abdomen.

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PLASMA CLOT SUTURE OF NERVES

EXPERIMENTAL TECHNIC

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By plasma clot suture it has been found possible in certain cases to effect better restoration of the anatomic relationships of nerve stumps with less trauma to them than with the aid of silk.¹ However, owing largely to imperfections in technic, our earlier experiments were not uniformly successful. It soon became clear that plasma clot was suitable as suture material only when the nerve ends could be united without tension. It developed that further requisites for satisfactory suture by means of a plasma clot are: freedom from hemorrhage and contusion around the site of suture; procurement of flat, smooth contact surfaces of the nerve stumps so that satisfactory coaptation of fibers can be obtained, and the use of a removable mold which permits the plasma to surround uniformly the entire site of suture.

The results of our efforts to bring about these favorable conditions for plasma clot suture of nerves in animals (rabbits, dogs and monkeys) together with an account of the development of a suitable mold will be given. The use of a special mold for suturing nerve grafts and a combined thread-plasma clot technic for suturing nerves under tension will be described.

OPERATIVE APPROACH TO THE SCIATIC NERVE

In our early operations on dogs, the sciatic nerve was exposed by an incision high in the posterior part of the thigh which split the biceps femoris muscle. In spite of the care which was taken to avoid trauma, some tearing of muscle fibers with bleeding occurred, both of which factors tended to increase the inflammatory and fibrotic reaction at the site of suture. A search for another approach to the sciatic nerve was made, and it was found that by making the incision of the skin laterally over the femur and incising the thin fascial extension of the biceps muscle one encounters a plane of cleavage between the biceps and the vastus lateralis muscle. By retracting the former mesially the sciatic nerve is exposed, and it may then be freed from the surrounding structures. Practically no tearing of muscle fibers follows this procedure, and by means of it the nerve can be exposed from a point 1 to 2 cm. distal to its exit from the pelvis to the popliteal fossa. All bleeding vessels should be caught and tied with fine silk ligatures. Since a bloody operative field promotes cicatrization at the site of suture, complete hemostasis is imperative.

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This work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the Jewish Hospital of Brooklyn. The work was also aided by a grant from the Committee on Scientific Research of the American Medical Association.

1. Tarlov, I. M., and Benjamin, B.: Plasma Clot and Silk Suture of Nerves, Surg., Gynec. & Obst. 76:366, 1943.

METHOD OF CUTTING AND ARRESTING BLEEDING FROM THE SCIATIC NERVE

Our former method of cutting the sciatic nerve consisted in elevating it, holding it taut by means of a nerve hook and severing it with a new razor blade. There were two chief disadvantages with this method: First, the amount of tension exerted on the nerve during its elevation and section in all probability resulted in damage for some distance from the cut. In the second place, the cut surfaces of the stumps were frequently uneven or one bundle of the nerve would retract more than another so that only incomplete contact of the stumps could be effected by means of plasma clot suture. Our present technic requires the use of a special nerve holder, the

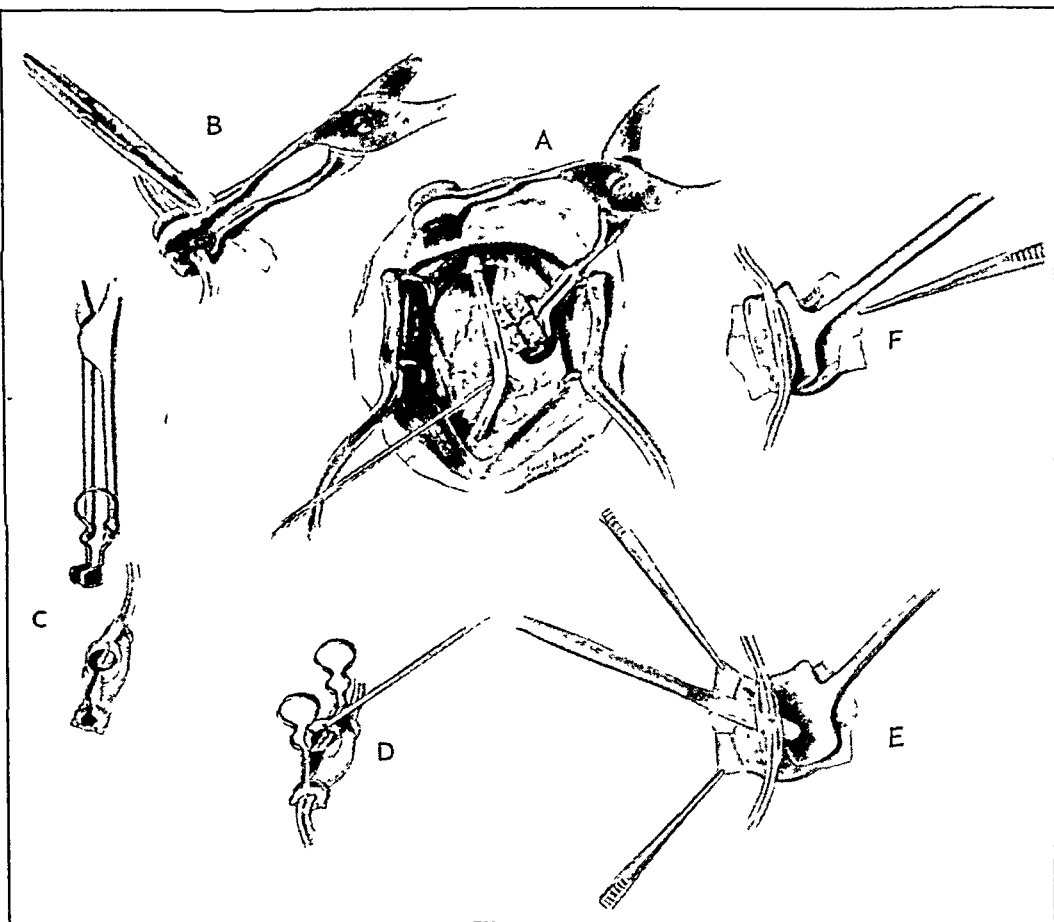


Fig. 1.—Series of sketches illustrating the technic of cutting the sciatic nerve and suturing it by means of plasma clot.

purpose of which is to hold the nerve securely while it is being cut. The device operates in a manner similar to a pair of scissors, but instead of cutting blades it has two arms equipped at the tips with opposed curved jaws covered with air-foam rubber, into which a groove is cut to accommodate the nerve (fig. 1 *A* and *B*). The use of the layer of air-foam rubber within the jaws of the instrument makes it possible to hold the nerve firmly without traumatizing it. A lengthwise slot about 25 mm. long and 0.5 mm. wide passes through the center of the jaws and the arms of the nerve holder to allow a razor blade to slide through and cut the nerve. The piece of razor used consists of one half of a Gillette type blade which

has been broken lengthwise and mounted on a needle holder. By this means one is enabled to obtain fairly flat cut surfaces on the nerve stumps, which permit a more accurate apposition of the severed ends. Furthermore, the danger of trauma to the nerve from tension, such as attended the use of the nerve hook, is eliminated. Also it was observed that there is less bleeding from the nerve stumps with the new technic.

Bleeding from the nerve stumps was controlled in our original experiments by means of gentle pressure with cotton pledgets. However, subsequent examination of the site of suture not infrequently disclosed infiltration with monocytic cells and giant cells around cotton fibers remaining adherent to the nerve. This tissue reaction made it difficult to assess the results of plasma clot suture in such instances. The use of cotton pledgets was therefore discarded, and the bleeding from the nerve stumps is now more readily controlled by means of small pieces of crushed autologous muscle. The pieces of muscle are removed after hemostasis has been attained. If contusion of the nerve ends has occurred or if the cut surfaces are ragged, a thin slice may be excised with the aid of the nerve holder and razor. Flat surfaces of the severed ends are essential for satisfactory coaptation. After a nerve has been divided, retraction of the epineurial sheath, with resultant prominence of the bundles of nerve fibers, sometimes occurs. This condition does not seem to retard successful regeneration following plasma clot suture, since a new connective tissue sheath is formed in the plasma clot.

USE OF RUBBER MOLDS FOR SUTURING NERVES WITH PLASMA CLOTS

At first, plasma clot suture on rabbits was performed merely by holding the nerve ends in apposition at the base of a trough formed by the neighboring tissues and then adding the plasma followed by the clotting agent. The main limitation of this method was that the plasma clot coated only the upper half of the nerve junction. It became clear that in order to make the union more secure, the technic had to be modified in some way so that the site of suture could be completely surrounded by the clot. A rubber mold was finally designed for this purpose.

Our early efforts at making a mold for containing the plasma at the site of suture resulted in a hollow tube wide open along its entire extent and with a cup-shaped depression in the center (fig. 2 *A*). The nerve was placed in the trough of the mold with the junction of the ends above the center of the cup. The chief fault with this mold was that it did not provide for adequate coating of the superior surface of the nerve. After the central cup was filled, any additional plasma tended to escape from the ends of the mold.

The next step in design of the mold was the introduction of gates into the trough on each side of the cup in an attempt to retain the plasma above the level of the line of suture (fig. 2 *B*). The gates were cut at one side to allow for removal of the mold after clotting of the plasma occurred. This type of mold proved unsatisfactory, because unless the openings under the gates were of exactly the same size as the nerve to be sutured the plasma escaped from these points. The next major step came with the development of a spherical mold with sleeves attached to envelop the nerve ends (fig. 2 *C*). An opening was cut in the top of the mold to permit manipulation of the nerve stumps and introduction of the plasma. A slit was made extending from the opening to the ends of the sleeves to allow for the application and removal of the mold. Leakage of plasma at the ends of the sleeve still occurred occasionally because of the variation in the size of the nerves to be sutured. Parallel fins of latex were then built upward from the slit (fig. 2 *D*). The fins were clamped together to obtain a closer fit around the nerve. Still leakage of plasma

from the ends of the sleeves sometimes occurred or else there was the possibility of damaging the nerve by too tight constriction of it in the sleeves.

At this point an experiment in a new type of mold was tried. A rigid aluminum mold was made on a lathe in two halves and held together by special metal hinged clips (fig. 2 *E*). It was thought that the construction of the mold in two halves, rather than in one piece, as in the case of the rubber molds, might facilitate its removal after clotting of the plasma had occurred. In the aluminum mold an oversized space was left in the sleeve and a layer of air-foam rubber inserted. The air-foam rubber afforded maximum cushioning effect on the nerve and prevented leakage of plasma around it. The difficulty in adjusting the four pieces of metal around the site of suture and the rigidity of the entire mold led us to discard it. However, the use of the air-foam rubber collar proved most helpful in solving the problem of constructing a rubber mold (fig. 2 *F*) suitable for use with nerves of a limited variety of sizes and also in preventing leakage of plasma from the ends of the mold without injurious constriction of the nerve. The air-foam rubber was

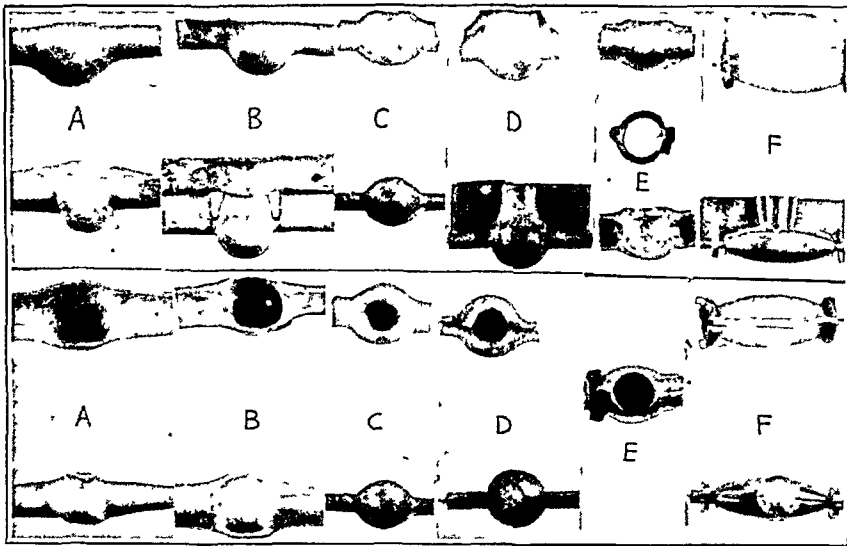


Fig. 2.—Photographs of the various molds and the models from which they were formed tried out in the development of the present mold used for suturing peripheral nerves. The two upper rows are side views; the two lower rows, top views.

thus incorporated into our rubber molds. The rubber molds, moreover, were made with a funnel opening on top so that when preliminary tests of plasma showed marked clot retraction an extra drop or two of plasma could be introduced into the funnel reservoir to insure that the clot would adequately cover the top of the suture. Another advantage of the funnel reservoir is that in those instances in which the plane of the nerve to be sutured is not perfectly horizontal the entire body of the mold can, nevertheless, be completely filled by introducing plasma to the top of the funnel.

The mold in its present form is shown in figure 3. In the sketch, *W* represents the wire supporting rails along which the nerve ends are placed. These supporting rails are threaded through wire loops in the base of the air-foam rubber collar, *A*. To hold the handles of the rails in place so that they can be easily grasped and removed during the operation, two wire loops (*L*) are placed on the outside of the air-foam rubber collar at one end of the mold. The loops are bent outward

so that they do not protrude unnecessarily far from the collars. The rails are made just long enough to reach from end to end of the mold. They are bent in the form shown. In the portion of the handle that fits into the loop is a series of ridges which prevents the rails from slipping out of place. The distance between the rails must not be too wide or the nerve ends may slip between them to the bottom of the mold. In order to facilitate insertion of the wire rails through the loops in the air-foam rubber collars, the shaft of a 26 gage hypodermic needle broken off from the hub and with its point blunted is used. The rails are threaded through these metal tubes after the latter have been introduced through the loops. The tubes are then withdrawn from the mold and the rails left in place.

In order to suture a nerve with plasma clot, one end of it is introduced into the mold with its cut surface in the center of the bowl (fig. 1 C). A metal clip (C) is applied to the fins (F) of the mold as close as possible to the collar. The clip thus tightens the grip of the collar around the nerve, preventing retraction of the nerve and leakage of plasma around it. The other end of the nerve is placed in the mold after the fins are spread apart by a forceps to facilitate introduction. When

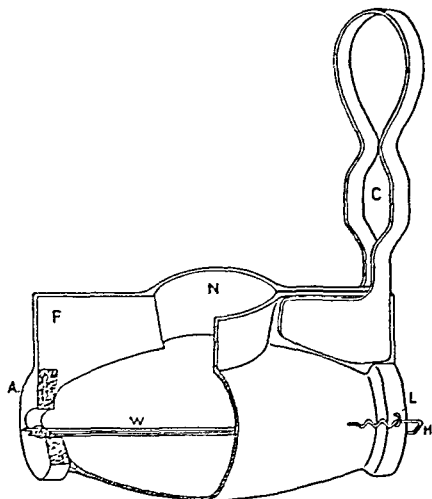


Fig. 3.—Diagrammatic sketch of the mold used at present.

satisfactory apposition of nerve ends has been obtained, a metal clip is applied to the fins at the other end of the mold. Plasma is then introduced into the mold through the funnel (N) (fig. 1 D). The large dorsal artery on the sciatic nerve serves as a convenient guide for maintaining the proper axial relationships between the central and peripheral nerve segments.

Before the use of the wire supporting rails was introduced, the nerve ends were held together with a small jeweler's forceps for about five minutes or until clotting had occurred. It was found to be very difficult to hold the nerve stumps together without any movements for this period of time, and, moreover, withdrawal of the forceps resulted in defects in the clot. The use of the wire supporting rails overcame these difficulties and enabled us to obtain better apposition of nerve ends. About twenty minutes after clotting occurs, which is the time required for plasma clots to achieve their maximum stability,² the wires are withdrawn by inserting

2. Goldfarb, A. I.; Tarlov, I. M.; Bojar, S., and Wiener, A. S.: Plasma Clot Tensile Strength: Its Relation to Plasma Fibrinogen and to Certain Physical Factors, *J. Clin. Investigation* 22:183, 1943.

forceps into the handles (*H*) of the wire rails and the metal clips are removed. The rails are made of very flexible no. 34 nickel silver wire, which may be curved acutely during their withdrawal without danger of their ends cutting the plasma clot.

The removal of the mold from the site of suture was the source of considerable difficulty in our earlier experiments. Finally an instrument was made by cutting down a teaspoon to the length of the mold and making it slightly concave to correspond to the shape of the clot around the junction in the nerve. After the clot is freed from the mold with the use of a small dissecting instrument, the fins of the mold are grasped by an assistant and held back. The spoon is then inserted between the mold and the sutured nerve (fig. 1 *E* and *F*). The nerve is gently elevated by the spoon and thus protected during the withdrawal of the mold by the assistant.

In those occasional instances in which the latex mold cannot be used because of the extreme smallness of the nerves or the lack of sufficient space, plasma clot suture can be used if one employs the original, cruder, technic described, namely, merely depressing the nerve ends into the neighboring tissues to form a trough in which the plasma can collect. As already mentioned, the ends must be held together with a fine forceps until clotting occurs.

EXPERIMENTS TO DETERMINE THE MOST SUITABLE SHAPE AND SIZE OF MOLD

After a suitable mold for retaining the plasma uniformly around the site of suture was developed, our attention became focused on the problem of distributing a given amount of plasma in such a way as to lend maximum support to the sutured nerve. The first question that arose was whether the basic shape of a mold would affect appreciably the strength of the nerve union. In order to test this point, experiments were performed *in vitro* on segments of freshly removed nerves sutured with autologous unmodified plasma in molds which were round, diamond shaped or fusiform. The nerves (all of the same general caliber and length) and the plasma were obtained from dogs, and the molds were all of approximately 15 drop capacity. The molds were so designed that 3 to 5 mm. of the nerve to each side of the suture was included in the plasma clot. The tensile strength of the sutured nerve was tested by the method described⁴ for testing plasma clots. Six tests were made with nerves sutured in each mold. The average weight load held by the nerve sutured in the fusiform mold was 22.5 Gm.; in the round and the diamond-shaped mold, 15 Gm. each. There is some indication, then, that the fusiform mold represents the best of the three shapes tried, since the junctions formed in it appear to be strongest.

The fact that the nerve slipped out of the clot rather than broke at the site of suture when the maximum weight was exceeded indicated that it might be possible to strengthen the union of the sutured nerve by increasing the segment of nerve gripped by the plasma, even though this entailed a reduction in the maximum diameter of the clot. Accordingly, three other fusiform molds of the same capacity were made and so shaped that 7 mm., 9 mm. and 11 mm. respectively of nerve on each side of the suture was gripped by the plasma clot. The average tensile strength of the nerve sutured in 17 tests in the mold of 10 mm. inside length was 24.1 Gm.; in 26 tests in the mold of 14 mm. size, 27.1 Gm.; in 27 tests in molds 18 mm. long, 28.5 Gm.; in 6 tests in 22 mm. molds, 25.8 Gm. The clot slipped off the

3. Footnote deleted.

4. Tarlov, I. M.; Goldfarb, A. I., and Benjamin, B.: A Method for Measuring the Tensile Strength and Stretch of Plasma Clots, *J. Lab. & Clin. Med.* **27**:1333, 1942.

nerve in every instance in which the nerves were sutured in the 10 mm. mold, while it invariably broke at the site of suture when the 22 mm. mold was used. These results indicate that the manner of distribution of a given amount of plasma affects the tensile strength of the sutured nerve to only a slight extent. Somewhat greater values for tensile strength were obtained with the 14 mm. and 18 mm. molds, and with them a balance seemed to have been reached between the point at which the clot slipped off the nerve and that at which the clot broke at the site of suture. Relatively little difference in the average weight load held before separation appeared at the site of suture occurred with the different molds, the average reading being about 8 Gm.

Experiments were then done to determine the effect of the amount of plasma on the tensile strength of the suture. A mold intermediate in size (16 mm.) between the 14 and 18 mm. ones was used as a basis for calculating the dimensional relationships for molds of larger capacities, since this mold required somewhat less exposure at operation than the 18 mm. mold. The ratio of inside diameter to length of the 16 mm. mold was 1:2.3. On the basis of this ratio, fusiform molds of the following approximate capacities were made: 7 drops; 13 drops; 25 drops; 36 drops; 45 drops; 90 drops. Nerves were sutured in vitro with use of these

Relationship of Capacity of Mold to Tensile Strength of Nerves Sutured with Plasma Clot

Capacity of Mold, Drops of Plasma	Average Weight Load Held Before Complete Separation Occurred at Site of Suture, Gm.	Average Weight Load Held Before Visible Separation Occurred at Site of Suture, Gm.	Number of Tests
7.....	16.3	2.5	8
13.....	30.6	5.6	9
25.....	36.3	9.2	6
35.....	60.3	16	6
45.....	68.6	?	11
90.....	83.6	?	7

molds, and tests of tensile strength of the sutured nerves were made. The results are shown in the table.

The average load which the nerve held before visible separation occurred at the site of suture was difficult to determine with the two largest molds, since the opacity of the large clots obscured the suture. Although considerable variation occurred in the tensile strength of nerves sutured with a given amount of plasma, the tendency toward a rise in weight load held with the increase in quantity of plasma which surrounded the nerve junction was fairly consistent in each series of determinations. These results are supported by previous test tube experiments which showed that the tensile strength of clots is directly proportional to their cross-sectional area.² From the standpoint of the strength of a sutured nerve, then, the greater the quantity of plasma used, the better the result. However, the limiting factor in determining the suitable amount of plasma that could be used proved to be the resultant histologic reaction.

Fifty-seven sciatic nerves were sutured in the six molds of different capacities, holding quantities of plasma which varied from 6 to 90 drops. The animals either died or were killed three to fifty-seven days after operation, and a quantitative comparison of the histologic reactions at the sites of suture was attempted. There was a lack of complete uniformity in the results, which suggested that one or more factors other than the quantity of plasma used tended to promote inflammation and fibrosis at the site of suture. Our experiments indicated that these factors

are trauma to the nerve ends or to surrounding tissue and hemorrhage during the operation. In certain instances these factors had more than offset the effect of the quantity of plasma used. Nevertheless, as a rule, it was found that with amounts of plasma up to 20 to 25 drops there followed minimal histologic changes, characterized by the appearance of a few polymorphonuclear leukocytes, lymphocytes, monocyctic cells, plasma cells, fibroblasts and thin-walled blood vessels. In most of the operations in which 90 drops of plasma was used and, to a much less extent in those in which 45 drops of plasma was used, considerable inflammatory reaction and, later, fibrosis ensued. Histologic changes of moderate intensity occurred with amounts of plasma in the intermediate range. Accordingly, approximately 20 drops of plasma was considered as a suitable amount for suturing the sciatic nerves of dogs. With care in performing the operation, somewhat larger quantities may be safely used.

THE USE OF DRIED PLASMA AND PURIFIED FIBRINOGEN FOR CLOT SUTURE OF NERVES

Autologous plasma was used for the sutures although homologous plasma would probably serve as well for this purpose. Our experiments have thus far revealed no difference in the degree of tissue reaction following suture with autologous and with homologous plasma clots. It has been our practice to use unmodified plasma (i. e. plasma to which no anticoagulant has been added), which is allowed to clot spontaneously, since it has been found that the addition of anticoagulants or coagulants to the plasma results in clots of diminished strength. In order to obtain unmodified plasma, the blood is collected in chilled paraffin-lined tubes packed in ice and centrifuged in large metal cups filled with ice; the plasma is then transferred to test tubes coated with paraffin and again packed in ice. In view of the inconveniences involved in the procurement of fluid unmodified plasma, experiments were undertaken in an attempt to prepare dried unmodified plasma which would not require a coagulant for clotting. The commercial dried plasma when dissolved in distilled water and recalcified yielded clots of rather low tensile strength. We have obtained dried plasma from dogs' unmodified plasma by the process of dehydration under high vacuum in the frozen state. However, like Strumia,⁵ we found that as a result of the drying process, the p_H of the plasma after being redissolved is increased and thereby the activity of the prothrombin is diminished, with resultant failure of spontaneous clotting. The addition of acid to the solution of dried plasma is necessary in order to restore the original p_H of the plasma and thus reactivate the prothrombin so that clotting can occur. In fact, after restoring the dried plasma to its original volume by dissolving it in distilled water and adding a small amount of dilute hydrochloric acid, fairly prompt clotting has been obtained and the clots proved to be almost as strong as those prepared from the original sample of fluid plasma. Hypertonic solutions of the dried plasma to which sufficient hydrochloric acid has been added to lower the p_H to approximately 7.4 have yielded some clots of greater tensile strength than those prepared from the original sample of plasma. Satisfactory nerve sutures have been obtained in dogs with clots prepared from dried unmodified plasma.⁶

Nerve sutures have been performed on dogs with clots formed from human fibrinogen and thrombin.⁷ Although clots prepared from these materials provided sufficient holding power for the nerve ends when tension was not present at the

5. Strumia, M.: Preservation of Prothrombin in Dried Plasma, J. A. M. A. **119**:710 (June 27) 1942.

6. The experiments with dried plasma are now being carried on with the assistance of Dr. A. E. Sobel and Mr. M. Rockemacher.

7. Supplied by Professor E. J. Cohn, Harvard University.

site of suture, unlike plasma clots they underwent some degree of lysis after twenty-four to forty-eight hours. This disadvantage is serious, since lysis of the clots may be followed by detachment at the site of suture because union of the nerve ends does not occur within this time. If this objectionable feature can be overcome, then fibrinogen-thrombin clots prepared from homologous blood may prove to be desirable as suture material for nerves. For the present, fresh fluid unmodified plasma seems preferable, although clots prepared either from dried plasma or from fibrinogen and thrombin may prove superior in the near future.

TECHNIC OF COMBINED PLASMA CLOT AND TANTALUM WIRE (OR SILK) SUTURE FOR NERVES UNDER TENSION

When nerve ends cannot be united without tension being present at the junction, then plasma clot suture is inadvisable since the risk of subsequent detachment at the site of suture is too great. It was suggested to one of us (I. M. T.) by Lieut.

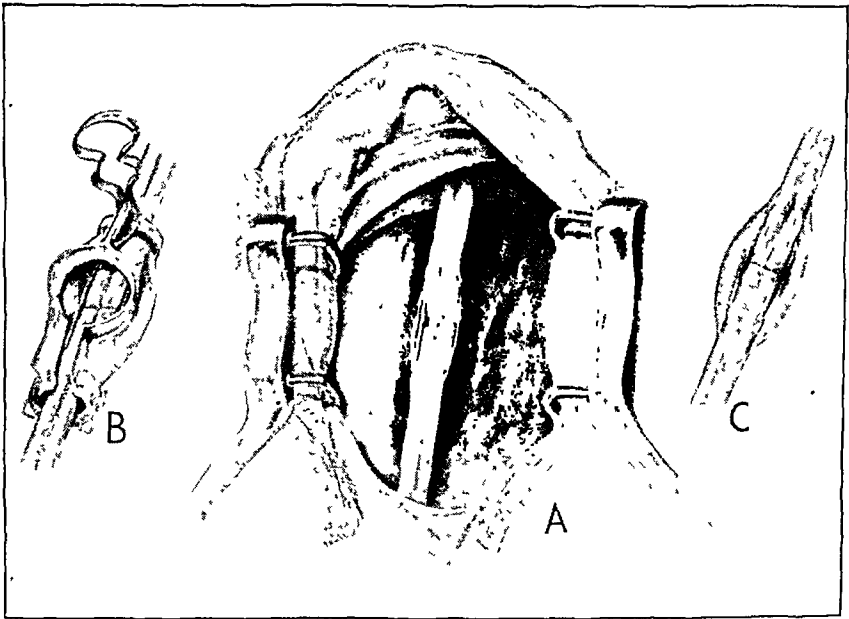


Fig. 4.—Technic of suturing a nerve under tension by use of tantalum wire and plasma clot.

Col. R. Glen Spurling that in those instances in which tension exists at the site of suture, fine tantalum wire⁸ (0.0025 or 0.0030 inch [0.0064 or 0.0076 cm.] in diameter) be used as tension sutures to approximate the nerve ends and plasma clot then used to achieve their accurate apposition. This suggestion was followed, and in other instances single strands of 00 Corticelli black silk untwisted into its three component strands were used instead of the tantalum wire. The wire or silk, threaded on fine curved ophthalmic needles, is introduced through the epineurium, one on each side of the nerve at the plane of its greatest diameter and at a distance of about 1 cm. from the ends of the nerve. The silk or wire is tightened until the nerve ends can be approximated without tension, and each is tied well away from the junction (figs. 4 *A* and 5 *A*). When one is dealing with small nerves which contain delicate connective tissue sheaths, some nerve fibers must be included in each bite of the suture in order to obtain sufficient hold on the

8. The Fansteel Metallurgical Corporation supplied the tantalum wire.

nerve to overcome the amount of existing tension. The nerve is then placed in the mold, the ends accurately adjusted on the wire rails (figs. 4 *B* and 5 *B*), the clips applied and the plasma introduced in the usual manner. By means of plasma clot suture, one is enabled to obtain more accurate coaptation of the cut surfaces without the buckling of nerve fibers or the distortion of nerve pattern that is apt to occur when any type of thread suture is used in an attempt to restore the anatomic relationships of a divided nerve. The two wire or silk sutures used to remove the tension from the suture are incorporated in the plasma clot (fig. 4 *C* and 5 *C*). The degree of inflammatory reaction is less with tantalum wire than with silk, and, moreover, the tantalum is stronger. Detachment at the suture site has been observed once in a series of 16 operations in which silk tension sutures were used in conjunction with plasma clot suture: in this one instance the silk sutures had broken. Breakage of the wire or separation at the suture site has not occurred in any of the 10 instances in which the tantalum wire-plasma clot technic



Fig. 5—Photographs taken at operation, showing the ends of the nerve approximated (*A*) by means of two tantalum wire sutures, accurately apposed (*B*) in the mold (one clip already in place) and sutured (*C*) with plasma clot. The tantalum wires are incorporated in the clot.

was used. Excellent apposition of nerve ends (fig. 6 *A*) with minimal tissue reaction (fig. 6 *B* and *C*) occurred with the use of this method.

It is to be emphasized that under conditions in which a great deal of tension exists at the site of suture the chance of successful results following any type of suture is probably small, and under such circumstances the insertion of some type of nerve graft should be considered.

TECHNIC OF SUTURING NERVE GRAFTS

If, owing to loss of nerve substance or to marked retraction, the ends cannot be apposed by the usual methods for diminishing nerve defects, such as the free mobilization of the ends or the flexion of a joint in order to relax a nerve, or by transposition of a nerve for the purpose of shortening the route that it must take,

then the insertion of some type of graft should be considered. If one accepts the prevailing viewpoint, that in order for satisfactory regeneration to occur a graft must contain viable Schwann cells—and there are good grounds for this belief⁹—then the use of grafts fixed in solutions, such as alcohol or a solution of formaldehyde, is to be condemned. One must focus, then, on the possibility of employing

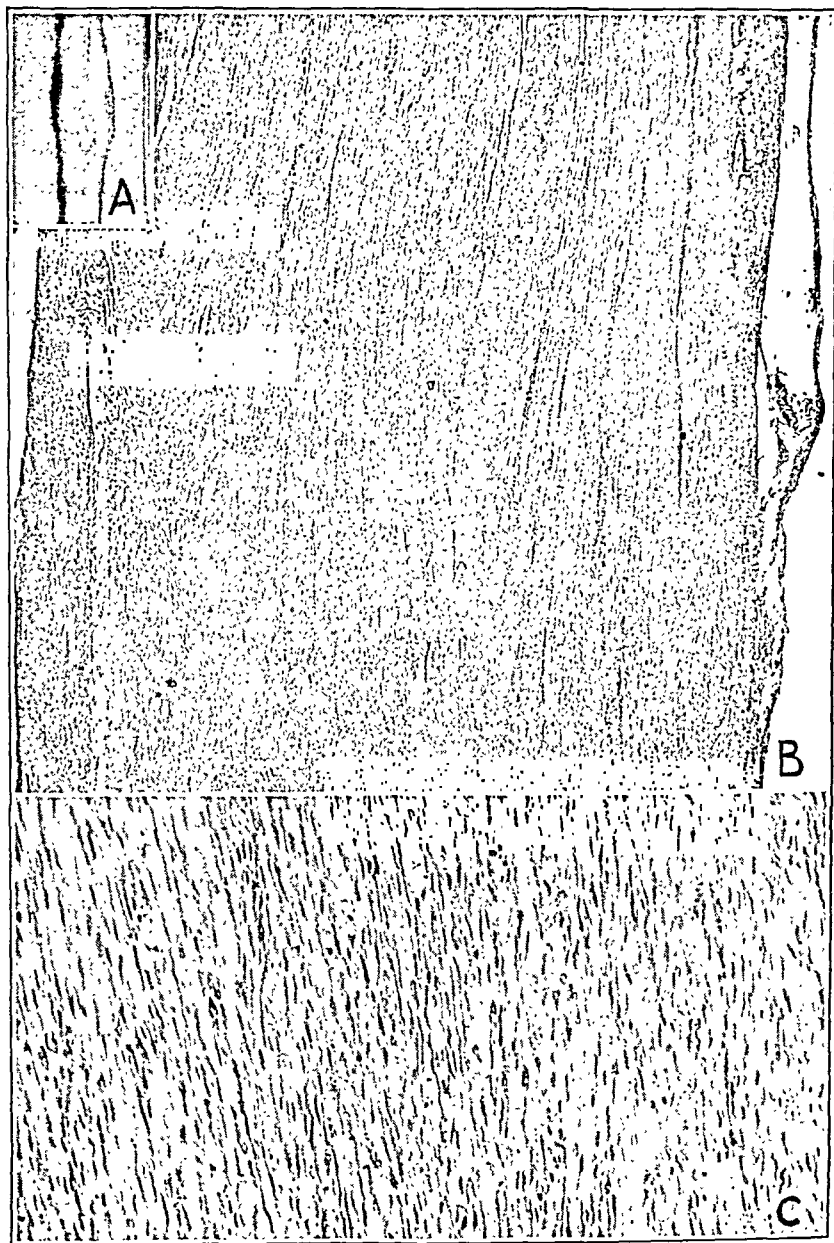


Fig. 6.—*A*, gross appearance of the sciatic nerve of a dog thirty-eight days after suture with tantalum wire and plasma clot; *B*, and *C*, photomicrographs from the site of suture, showing practically no inflammatory or fibrotic reaction. The sections were stained with hematoxylin and eosin (*B*, $\times 32$; *C*, $\times 180$).

9. Young, J.; Holmes, W., and Sanders, F.: Nerve Regeneration: Importance of the Peripheral Stump and the Value of Nerve Grafts, *Lancet* 2:128, 1940.

viable nerve transplants. As was to be expected in view of the high degree of specificity of mammalian tissues, heterologous nerve grafts have not proved successful. Although the possibilities of using viable homologous nerve grafts have not yet been thoroughly explored, experimental laboratory and clinical observations suggest that the most satisfactory results may be obtained with the use of autologous grafts. When defects exist in large nerves, the only type of autologous graft that could be considered is the cable transplant, since with a human subject there would be no justification for sacrificing one major functioning nerve for another. In cable transplantation, several segments of a nerve which can be sacrificed without serious resultant defect are used. These segments are placed side by side until their combined cross-sectional area approximates that of the nerve to be repaired. A tubular mold made of latex and containing the inside shape and transverse measurements of the desired cable has proved useful for the formation of the cable graft. The nerve segments are glued together by means of a thin coat of plasma applied with a pipet. The graft should be made a few millimeters longer than required, so that a thin slice can be excised in order to obtain a flat contact surface for apposition with the freshly cut ends of the nerve stumps of the host.

To facilitate the introduction and suture of a nerve graft, a special tandem (twin) mold was made. The mold consists of two of the single molds already

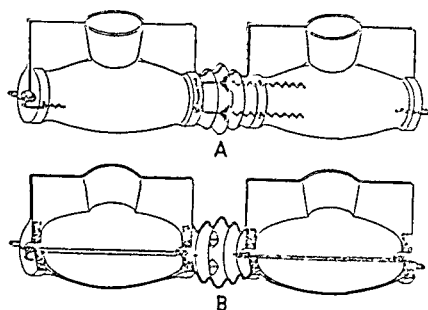


Fig. 7.—Sketches of the exterior (A) and interior (B) of the twin mold used for suturing nerve grafts by means of plasma clot. Recently 16 gage spring sheet nickel silver has been used to make the adjustment regulators. The closed ends of the U are fastened with fine wire to the outside of one of the air-foam rubber collars next to the adjustment bellows. The prongs are made so that they spring slightly apart, thus causing notches cut 1 mm. apart on the outer side of each prong to catch on the sides of the wire loops.

described with a bellows between them, all made into one piece (fig. 7). The distinctive feature of the tandem mold is the bellows, which allows of some adjustment between the two main body parts of the mold in order to accommodate grafts of varying sizes. The bellows is similar to a miniature camera bellows but circular in form, wider at the center and tapering at both ends. This mold permits the insertion of the graft into it before the mold is placed into the operative site between the nerve ends, thus rendering the procedure simpler than it would be if attempted with two single molds. The distances between the centers of the two main parts of the body of the mold with bellows collapsed and extended are 30 and 40 mm. respectively. The mold can therefore be used for grafts which vary in length from 3 to 4 cm. For longer grafts bellows of correspondingly greater lengths may be used. Grafts of 2.5 and 3 cm. in length may be sutured in special twin molds which contain, instead of the median bellows, a single median air-foam rubber collar, the width of which depends on the length of the graft. Grafts of less than 2.5 cm. in length may be sutured in single molds

which contain two funnels, one above the site of each suture, the mold being longer than the single mold previously described but somewhat constricted in the center. In order to adjust the tandem mold to a desired length and prevent tension on the graft or the sutures, two U-shaped wires with undulations along their prongs are slipped through small wire loops in the proximal collars of the mold. A notch is cut away from the central fold of the bellows so that it will clear the wires. Because of angulation of the undulations, the adjustment wires prevent change in length when the bellows has been placed in a certain position. The wire supporting rails on which the nerve ends rest, as used in the single mold, are contained in each half of the mold.

After the ends of the nerve graft are properly apposed to those of the host nerve, the four metal clips are applied to the fins as close as possible to the air-foam rubber collars and the plasma introduced through each funnel. After complete clotting has occurred, the wire supporting rails are withdrawn, the clips are removed and the mold, freed from clot and nerve in the usual way, is withdrawn with the aid of a spoon the length of the mold. A graft sutured in this way is shown in figure 8.



Fig. 8.—Photograph taken at operation on a dog, showing a single homologous cadaver graft sutured with plasma clot. Pronounced retraction of the clot has occurred, so that there is little excess clot left around the sites of suture.

COMMENT

The most important factors in the technic of suturing nerves are the accurate restoration of fascicular topography and the utilization of materials and methods which result in the production of a minimum amount of cicatrization at the site of suture. An apparently perfect end to end approximation of the severed nerve ends may result in incomplete functional recovery if torsion of the stumps has occurred, because regenerating motor nerve fibers might enter channels leading to sensory end organs and conversely. It seems likely that such misdirection of nerve fibers accounts for many of the defective end results from nerve suture. Although accurate alinement of nerve fibers in a microscopic sense is probably impossible to achieve, a closer approach to this ideal may be obtained with plasma clot than with silk suture. The nerve ends can be adjusted in the mold before the clips are applied, and more exact alinement can be made, even after the clips have been applied, by utilizing the slight natural stickiness of the nerve ends to maintain the relationship of the stumps until the plasma is added and the junction

made more secure. Unless loss of nerve substance has occurred, matching of blood vessel markings, longitudinal striations or nerve bundles makes it possible to restore the proper axial relationships of the nerve stumps when plasma clot suture is used. Such realinement of nerve trunks is not as readily achieved by means of silk suture, since it is difficult to place each stitch at exactly corresponding circumferential points along the stumps. As a result some degree of torsion is likely to occur; moreover, crowding of nerve fibers, with distortion of nerve pattern, frequently occurs when the threads are tied.

Careful attention must be devoted to the prevention of scarring at the site of suture, since such proliferative changes in connective tissue constitute a considerable hindrance to the downgrowth of nerve fibers. The use of fine silk thread confined to the epineurium results in relatively little inflammatory and subsequent fibrotic reaction at the site of suture. However, in the case of small nerves which possess delicate connective tissue sheaths, it is difficult or impossible to confine the stitches to the epineurium, and strangulation of nerve tissue with subsequent necrosis and fibrosis frequently results. Young and Medawar¹⁰ have sought to overcome this difficulty by introducing the use of fortified cockerel plasma and chick embryo extract for the purpose of joining ends of divided nerves. Our studies¹¹ have shown that autologous plasma is superior to cockerel plasma and chick embryo extract as suture material in that less inflammatory and fibrotic reaction occurs. Autologous plasma compares favorably with and usually surpasses fine black silk suture in respect to the small amount of resultant inflammation and scarring.

The use of plasma clots obviates much of the cicatrization resulting from strangulation of tissue which accompanies the use of any type of thread suture employed for the purpose of bringing nerve ends into apposition. The greater degree of handling of the nerve ends entailed by the use of thread rather than clot suture contributes to the trauma and scarring of tissue at this site. It is to be expected that with careful technic in the execution of autologous plasma clot suture formation of scar tissue at the site of junction may be reduced to a minimum.

It must be borne in mind that the real test of the value of a new technic for suturing nerves is not the type of histologic reaction that occurs at the suture site nor the appearance of numerous nerve fibers in the peripheral stump but rather the degree to which restoration of function to the innervated part occurs. In this connection, it should be stated that several dogs on which plasma clot suture of the sciatic nerve was done on one side and silk suture on the other side have shown almost complete restitution of normal gait. In these few animals there has been as yet no consistent difference in the rate or degree of recovery of function which could be attributed to the different methods of suture. However, the superior gross and histologic results associated with plasma clot would lead one to anticipate correspondingly better functional return to the innervated part than with silk suture; further correlative studies will be necessary to test this point.

CONCLUSIONS

When performed in the manner described, autologous plasma clot suture of peripheral nerves has proved experimentally to be a useful procedure in those

10. Young, J. Z., and Medawar, P. B.: Fibrin Suture of Peripheral Nerves, *Lancet* **2**:126, 1940.

11. Tarlov, I. M., and Benjamin, B.: Autologous Plasma Clot Suture of Nerves, *Science* **95**:1258, 1942; footnote 1.

instances in which the stumps can be approximated easily without any tension. It is possible to obtain more accurate apposition of nerve ends with better restoration of fascicular topography by this means than with thread, and, moreover, less scarring is apt to occur at the junction. Good functional return to the innervated part follows the use of this technic on dogs.

When a moderate degree of tension does exist at the line of suture, it is still possible to utilize the advantages of plasma clot suture by combining this technic with the use of very fine tantalum wire tension sutures. The thread sutures are introduced well away from the cut surfaces of the nerve and serve to eliminate the factor of pull from the nerve junction.

A tubular mold has been found useful for the formation of cable grafts from single strands of nerve glued together with clotted plasma. The technic of suturing single or cable grafts is greatly facilitated by the use of the twin mold described.

Miss Dorothea Denslow, director of the Clay Club of New York, assisted in the development of the mold for use in the technic of plasma clot suture. Miss Ruth Kaslow assisted at the operations and in the postoperative care of the animals.

MECHANISM OF ERYTHREMIA

ERYTHREMIA RESULTING FROM TRAUMATIC SHOCK IN DOGS AND FROM
INJECTIONS OF EPINEPHRINE INTO HUMAN BEINGS AND DOGS

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Epinephrine administered intravenously to dogs causes the hematocrit index to rise, probably because of contraction of the spleen.¹ A similar rise which occurs in traumatic shock is diminished by section of the spinal cord or spinal anesthesia. The relationship of these facts was brought to our attention because of the observation that the spleens of dogs which had died of traumatic shock were small and bloodless.

It seemed probable that sympathetic stimulation of the spleen might in part be responsible for the erythremia of traumatic shock in dogs. It has been attempted, therefore, to show that exclusion of the spleen by pharmacologic and surgical means reduces the anticipated increase in hematocrit index when shock is elicited by tourniquets or intestinal manipulation. Further, the question has been explored as to the importance of the spleen in the erythremia resulting from injections of epinephrine into normal and splenectomized human beings, on the assumption that epinephrine to some extent reproduces the blood picture which may be obtained in shock.

METHODS

All animals were anesthetized with pentobarbital sodium (30 mg. per kilogram of body weight administered intraperitoneally). Blood pressure was recorded with a mercury manometer and a kymograph connected to a cannulated carotid artery. Heparin solution and 10 per cent sodium citrate were used as anticoagulant. Six normal and 4 splenectomized dogs were each given 10 to 15 cc. of a $\frac{1}{10,000}$ solution of epinephrine hydrochloride intravenously over a period of sixty minutes. Splenectomy was done from one to seven days before the experiments were begun. Six normal human beings and 6 human beings whose spleens were removed after trauma or because of hemolytic jaundice were given 2 mg. of epinephrine hydrochloride in such a manner that the arterial pressure was maintained for forty-five to sixty minutes at 180 to 220 mm. of mercury systolic and 100 to 120 mm. of mercury diastolic. Thirty minutes before the epinephrine was administered, 0.4 Gm. of seconal sodium (sodium allyl-[methylpropylcarbonyl]-barbiturate) was given by mouth. This procedure was controlled by repeating the process in 6 normal persons with physiologic solution of sodium chloride substituted for the epinephrine solution.

Tourniquet shock was induced by applying four strands of ordinary package twine about the hindlimbs above the greater trochanter laterally and as high as possible medially. These were pulled tightly by hand so that partial venous and arterial occlusion resulted. The cords were cut at the end of four hours. Fifteen normal dogs, 12 splenectomized dogs and 6 dogs whose pressor response to epinephrine was reversed to depressor by intravenous injection of piperidomethyl-3-benzodioxane (Fournau 933) were used. Reversal of the response to epinephrine was produced before giving the drug by infusing 8 to 10 cc. of solution containing 10 mg. of piperidomethyl-3-benzodioxane per cubic centimeter and was maintained for five to seven hours by a continuous drip of 6 to 8 drops per minute.

From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital.

1. (a) Barcroft, J., and Barcroft, H.: *J. Physiol.* **58**:138, 1923. (b) Cruickshank, E. W. H.: *ibid.* **61**:455, 1926. (c) Hargis, E. H., and Mann, F. C.: *Am. J. Physiol.* **75**:180, 1925. (d) de Boer, S., and Carroll, D. C.: *J. Physiol.* **59**:312 and 381, 1924. (e) Hanak, A., and Harkavy, J.: *ibid.* **59**:121, 1924.

To minimize the factor of loss of fluid into the injured areas, plaster casts were applied to the limbs with tourniquets on them. They were put on one hour before the experiment and extended to the level at which the cords had been applied. Six normal dogs, 4 splenectomized dogs and 4 dogs whose response to epinephrine had been reversed with intravenous injections of piperidomethyl-3-benzodioxane were used in these experiments.

Shock was produced in 10 normal dogs and 10 splenectomized dogs by gently manipulating the intestines for twenty-five minutes and leaving them exposed until death of the animal.

Hematocrit indexes were determined by the Wintrobe method with heparinized blood. Blood was drawn from the femoral artery in the dogs and from an antecubital vein without stasis in the human subjects.

RESULTS

1. *Effect of Intravenously Administered Epinephrine in Normal and Splenectomized Dogs and Human Beings.*—These results are illustrated graphically in chart 1 and tabulated in tables 1 and 2. One to 1.5 mg. of epinephrine hydrochloride given intravenously over a period of sixty minutes to 6 anesthetized

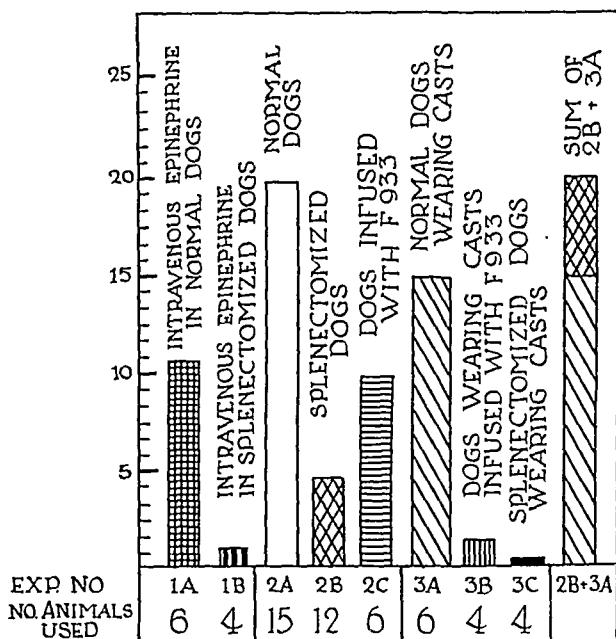


Chart 1.—Rise of hematocrit index observed in dogs after intravenous administration of epinephrine and during tourniquet shock in normal and splenectomized dogs and in dogs given an infusion of piperidomethyl-3-benzodioxane, both with and without casts.

normal dogs with an average hematocrit index of 38.5 mm. increased this average by 10.5 mm. (maximum 13 mm.; minimum 7 mm.). Further injections of epinephrine caused no greater rise in index. The same procedure carried out with 4 splenectomized dogs whose average hematocrit index was 34.4 mm. caused an average rise of 0.9 mm. (maximum 2 mm.; minimum 0.5 mm.) Thus the results sharply divided the splenectomized and nonsplenectomized animals.

Six normal human beings received 2 mg. of epinephrine hydrochloride intravenously at a rate rapid enough to maintain arterial blood pressure between 180 and 220 mm. of mercury systolic and 100 and 120 mm. of mercury diastolic for forty to sixty minutes (table 1). The average increase in hematocrit index in this group was 3.5 mm., which compares with a rise of 1.1 mm. in 6 splenectomized persons (table 2) subjected to the same procedure. The 6 normal control subjects

TABLE 1.—Representative Experiments on Dogs and Patients Receiving Epinephrine Intravenously and Dogs Put into Shock with Tourniquets and by Intestinal Manipulation

Experiment	Length of Experiment in Hours	Stage						Result
		Initial		Middle		Terminal		
		Arterial Blood Pressure, Mm. Hg	Hemato-crit Index, % of R. B. C.	Arterial Blood Pressure, Mm. Hg	Hemato-crit Index, % of R. B. C.	Arterial Blood Pressure, Mm. Hg	Hemato-crit Index, % of R. B. C.	
Intravenous injection of ephinephrine								
Normal dog.....	1.0	180	44	305	52.0	200	56.0	Lived
Splenectomized dog.....	1.0	145	31	200	32.0	200	33.0	Lived
Intravenous injection of ephinephrine								
Normal human being.....	1.0	102/60	40.5	180/ 90	44.1	160/80	43.7	Lived
Splenectomized human being.....	1.0	114/90	55.0	230-120	54.5	170/90	56.0	Lived
Tourniquet shock								
Normal dog.....	10.0	136	37.0	104	55.5	80	62.0	Died
Splenectomized dog.....	6.5	142	46.0	98	48.0	80	50.5	Died
Dog given infusion of piperidomethyl-3-benzo-dioxane.....	4.5	148	46.0	100	51.0	46	52.0	Died
Tourniquet shock of dogs wearing casts								
Normal dog.....	6.0	145	40.0	104	55.0	120	56.0	Lived
Splenectomized dog.....	9.5	138	52.0	108	54.5	128	53.0	Lived
Dog given infusion of piperidomethyl-3-benzo-dioxane.....	8.0	132	33.5	74	36.0	50	36.0	Lived
Intestinal stripping shock								
Normal dog.....	9.75	170	42.0	105	54.0	36	63.0	Died
Splenectomized dog.....	5.5	120	31.0	68	32.5	26	39.0	Died

TABLE 2.—Changes in Hematocrit Index in Human Beings Following Intravenous Administration of Two Milligrams of Epinephrine

Normal Subjects Given Physiologic Solution of Sodium Chloride				Nonsplenectomized Patients				Splenectomized Patients			
Patients and Diagnosis	Time, Minutes	Arterial Blood Pressure, Mm. Hg	Hematocrit Index, % of R. B. C.	Patients and Diagnosis	Time, Minutes	Arterial Blood Pressure, Mm. Hg	Hematocrit Index, % of R. B. C.	Patients and Diagnosis	Time, Minutes	Arterial Blood Pressure, Mm. Hg	Hematocrit Index, % of R. B. C.
No. 1	0	110/70	44.0	No. 1, R. C.	0	132/86	38.0	No. 1	0	120/80	42.4
W. S.	15	104/70	43.4	carbon	5	240/120	38.5	W. R.	15	190/110	42.4
normal	30	110/70	44.5	tetra-	20	200/120	41.5	familial	30	190/110	43.0
	50	114/74	44.8	chloride	30	200/120	41.5	hemolytic	45	180/110	43.4
				poisoning				jaundice..	60	200/110	43.0
No. 2	0	108/62	48.0	No. 2, H. B.	0	102/60	40.5	No. 2, D. I.	0	114/90	55.0
R. T.	15	108/80	48.5	orthostatic	15	180/90	43.5	gunshot	15	230/120	55.5
normal	30	108/70	47.0	albumi-	35	190/100	44.2	wound of	30	215/110	56.0
	50	108/62	47.0	nuria	50	180/90	43.7	spleen	50	200/100	55.0
No. 3	0	108/70	39.0	No. 3	0	136/80	29.0	No. 3	0	136/80	46.0
E. B.	15	104/68	38.0	H. P.	15	216/100	32.5	M. K.	15	190/110	45.0
normal	30	104/70	38.0	secondary	30	190/90	31. 5	hemolytic	30	200/100	46.0
	50	108/68	38.0	anemia	50	196/100	30.5	anemia	50	180/100	46.0
No. 4	0	138/90	30.5	No. 4	0	116/70	30.5	No. 4, J. O.	0	136/70	48.0
L. F.	10	136/92	31.8	J. W.	15	170/100	32.5	gunshot	20	200/100	49.0
4 months	30	138/94	30.5	6 months	30	180/100	33.0	wound	30	190/96	48.0
pregnant	45	126/96	32.0	pregnant	50	160/90	34.0	of spleen	50	196/90	48.0
No. 5	0	124/60	32.5	No. 5	0	110/70	41.0	No. 5, S. J.	0	110/70	47.2
L. C.	10	126/70	32.0	M. D.	25	180/120	41.2	gunshot	20	200/110	48.2
normal	30	124/62	31.5	ovarian	45	190/120	42.0	wound	40	190/106	48.3
	40	124/64	32.0	cyst	55	186/130	43.0	of spleen	55	160/100	48.3
No. 6.	0	116/68	39.0	No. 6	0	116/80	34.0	No. 6, L. S.	0	130/190	49.0
J. J.	15	115/68	39.2	C. G.	20	180/118	34.6	thrombo-	15	180/110	48.8
normal	30	116/70	38.6	psycho-	45	190/122	37.0	cytopenic	30	160/120	45.0
	45	116/70	39.0	neurosis	55	180/126	38.0	purpura	50	126/70	50.0
Average increase.....			0.8				3.4				1.1

receiving physiologic solution of sodium chloride had an average rise in hematocrit index of 0.8 mm. Thus reasonable accuracy of the method was demonstrated.

2. *Effect of Tourniquet Shock on Anesthetized Dogs, Splenectomized Dogs and Dogs Given an Infusion of Piperidomethyl-3-Benzodioxane.*—Results of representative experiments of tourniquet shock induced in normal anesthetized dogs, splenectomized dogs and dogs given infusions of piperidomethyl-3-benzodioxane are presented in table 1. During the four hours the tourniquets were in place, swelling of the limbs and varying degrees of hypotension occurred. Occasionally an animal died in shock as early as two hours after application of cords. The arterial pressure fell to 80 to 90 mm. of mercury at the end of four hours in some animals, which maintained this level for six to eight hours and died eleven to fourteen hours after the beginning of the experiment. However, the usual picture consisted of a fall in blood pressure to 100 mm. of mercury during the period of vascular occlusion, followed by a precipitous fall of 20 to 40 mm. immediately following release of the constricting cords. This fall continued more slowly until the animal's death, after two to five hours. This average experiment was usually easily reproducible.

In 15 normal dogs the average hematocrit index was 40.8 mm. Tourniquet shock in these animals resulted in an average rise of 19.9 mm. from the beginning of the experiment to its ending by death (maximum 29 mm. and minimum 12 mm.). The same type of shock in 12 splenectomized dogs gave the less striking rise of 4.3 mm. from an initial index of 36.5 mm.

Six dogs receiving piperidomethyl-3-benzodioxane intravenously before induction of tourniquet shock exhibited an average increase in the index of 9.6 mm. (maximum 11.5 mm. and minimum 6.0 mm.) (chart 1).

Normal animals put into shock by the tourniquet method manifested 60 to 75 per cent of the total rise in the hematocrit index during the first hour of the experiment. Dogs given an infusion of piperidomethyl-3-benzodioxane had 40 to 50 per cent of the total rise in the index during the first one to two hours of the experiment. The remaining increase became evident gradually and evenly during the course of the experiments. In splenectomized animals no early sharp rise in the index was noted; the entire change was gradual. These findings point to a mechanism capable of delivering a large volume of red cells into the circulation. Piperidomethyl-3-benzodioxane, a sympathetic-paralyzing drug, partially inhibits this function, and splenectomy abolishes it, converting the changes into a gradually rising curve. Splenectomy did not, however, completely abolish hemoconcentration in animals shocked by the tourniquet method. The most obvious additional mechanism was local loss of plasma into the legs below the occluding tourniquets. To exclude this, plaster casts were applied to the hindlimbs and all experiments were repeated.

3. *Effect of Tourniquet Shock on Anesthetized Normal Dogs, Splenectomized Dogs and Dogs Given an Infusion of Piperidomethyl-3-Benzodioxane, All of Which Wore Casts on Their Hindlimbs.*—Results of tourniquet shock induced in normal anesthetized dogs, splenectomized dogs and dogs given an infusion of piperidomethyl-3-benzodioxane, all of which wore casts, are shown in chart 1, and representative experiments are recorded in table 2.

In this group of 14 dogs there was usually a gradual fall in arterial blood pressure from an average of 150 mm. of mercury to approximately 100 mm. of mercury during the first four hours. When the cords were released there was an abrupt but transient fall of 15 to 30 mm. of mercury. No further decline of pressure was noted. Fifty per cent of animals died forty-eight to ninety-six hours later with gangrenous changes in the legs, and the remaining animals survived.

The 6 control animals in this group showed an average rise in hematocrit index of 14.8 mm., 90 per cent of which occurred in the first quarter of the experiment (maximum 22 mm.; minimum 9 mm.), contrasting sharply with splenectomized dogs wearing casts, which experienced an average rise of 1.2 mm., and with 4 dogs with casts that were given an infusion of piperidomethyl-3-benzodioxane which had no rise.

4. *Effect of Shock Induced by Intestinal Stripping of Anesthetized Normal and Splenectomized Dogs.*—Representative experiments of this group are found in table 1. After twenty-five minutes of gentle manipulation of the intestines the arterial blood pressure fell from an average of 160 to approximately 110 mm. of mercury. This pressure was usually maintained for five to eight hours by the normal dogs and for three to five hours by the splenectomized dogs. The pressure then began to fall, reaching 60 to 80 mm. of mercury after one to two hours. Death usually occurred within the next two hours.

As with tourniquet shock, 50 per cent of the rise in the hematocrit index occurred during the first hour of the experiment. This immediate rise was not

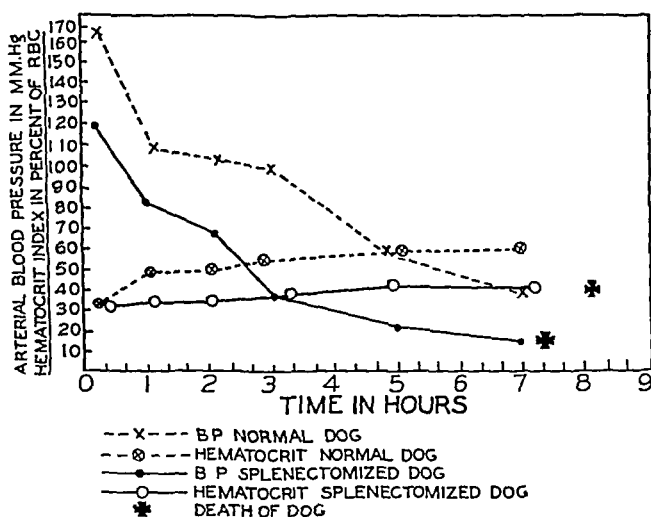


Chart 2.—Time relation of rise in hematocrit index for normal and for splenectomized dogs put into shock by intestinal manipulation.

noted in splenectomized dogs, in which all of the hemoconcentration developed gradually during the course of the experiment (chart 2).

Ten anesthetized normal dogs put into shock by intestinal stripping exhibited an average increase in hematocrit index of 26.0 mm. from an initial average index of 35.4 mm. (maximum 31 mm.; minimum 23.5 mm.), as compared with 10 splenectomized dogs under the same conditions, which showed an average increase of 13.4 mm. Thus 12.6 mm. is left to be accounted for by splenic participation.

REVIEW OF THE LITERATURE AND COMMENT

There is abundant evidence that the spleens of animals contract in response to various stimuli discharging highly cellular blood into the general circulation. In 1830 Dobson² first showed that the volume of dogs' spleens increased considerably following large feedings. He postulated that the spleen acted as a

2. Dobson, W.: An Experimental Inquiry into the Structure and Function of the Spleen, London, J. Wilson, 1830.

storage chamber for blood, thereby protecting the vascular system from sudden changes in blood volume, as during digestion. Wagner in 1849³ and Sabinski in 1865⁴ demonstrated contractibility of the canine spleen. This was shown to be of nervous origin by Schiff,⁵ who elicited it in rabbits and cats by stimulating the splanchnic nerves and the semilunar ganglions. That nervous stimuli other than sympathetic could cause splenic contraction was shown in 1868 by Oehl,⁶ who demonstrated it by stimulating the peripheral end of either vagus nerve in dogs, rabbits and cats. Tarchanoff⁷ and Bulgak⁸ caused splenic contraction by stimulation of the medulla. Roy⁹ confirmed most of these observations in 1880 and added plethysmographic studies. He demonstrated rhythmic contractions normally present that varied considerably, increasing particularly during hypotension and with the appearance of Taube-Hering waves. He produced splenic contraction by stimulating either end of a cut sensory nerve. Schäfer and Moore¹⁰ found the spleens of dogs responsive to changes in blood pressure and to asphyxia and epinephrine. They studied the nerve supply of the spleen and found it received both motor and inhibitory fibers through the splanchnic nerves. The motor fibers arose from the third thoracic to the first lumbar but chiefly from the fifth to the tenth thoracic segment. Hargis and Mann¹¹ studied changes in volume of canine spleens with the plethysmograph. They used food, excitement and epinephrine as stimuli to prove that splenic contraction was due to a vasomotor mechanism which could be abolished by splenic denervation. The intrasplenic pressure produced by contraction was measured by Richberg,¹¹ who tied off the blood supply to and from the organ and found an average rise of 70 to 80 mm. of mercury following electrical stimulation of the splenic nerves.

Barcroft and his co-workers,¹² Hanak and Harkavy,¹² Cruickshank^{1b} and others¹³ have gathered evidence that the spleen contracts in response to carbon monoxide poisoning, hemorrhage, exercise, rebreathing and injection of an epinephrine solution or of solution of posterior pituitary, and that this contraction discharges an extra supply of erythrocytes into the circulation. Their studies were conducted in the main on dogs and cats but included rabbits, horses and monkeys.

Contraction of the spleen is apparently a well established vasomotor mechanism responding to varied stimuli. There is also evidence indicating that such activity delivers highly cellular blood into the circulation. In 1908 Boveri¹⁴ and in 1912

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14. Boveri, P.: *Biophysikal. Centralbl.* **3**:511, 1907-1908.

Steiger¹⁵ reported polycythemia in dogs following injection of epinephrine. Lamson¹⁶ reported a 25 to 39 per cent increase in red blood cell counts of cats following excitement, a response prevented by adrenalectomy. Izquierdo and Cannon¹⁷ in 1928 confirmed the occurrence of emotional polycythemia in cats and prevented it by splenic denervation.

Barcroft and Poole^{12c} added a valuable link to this chain of evidence indicating that splenic contraction results in the polycythemia found after epinephrine, excitement, anoxia and food by experiments showing splenic blood to be at least 50 per cent richer in hemoglobin than peripheral blood. This work supported similar reports of Cruickshank^{1b} and Scheunert and Krzywanek.¹⁸

Kendrick and Uihlein¹⁹ applied this principle to dogs in shock. Their animals were anesthetized with ether and put into shock by intestinal manipulation. Midway in the experiment ether anesthesia was replaced by use of sodium pentobarbital. The nonsplenectomized dogs had a decrease in hematocrit index, presumably due to splenic relaxation. The change of anesthetic for splenectomized animals produced no such difference. Hausner, Essex and Mann²⁰ outlined the spleen with pellets of lead by the method of Barcroft and Harris. They observed contraction in animals under ether anesthesia that resulted in polycythemia. When sodium pentobarbital was substituted for ether anesthesia the spleen was seen to relax, with a resulting decided reduction of the red blood cells in the peripheral blood.

This body of evidence was doubted by Hahn, Bale and Bonner,²¹ who used radioactive iron to study red blood cell mass (volume of circulating red blood cells). They found no increase in red cell mass after injecting epinephrine intravenously into normal anesthetized dogs and concluded that the rise in hematocrit index could not be due to discharge of red cells previously stored in the spleen. However, they, as have others, found that splenectomy abolished the increase in hematocrit index following injection of epinephrine. This being true, their results might be questioned.

As regards splenic participation in the hemoconcentration of shock, Keeley, Gibson, and Pijoan²² found that splenectomy abolished it in burn shock. Searles and Essex²³ and Essex, Seeley, Higgins and Mann²⁴ demonstrated that anesthesia induced with barbiturates caused hemodilution due to splenic relaxation with consequent removal from free circulation of large volumes of red cells. Moon²⁵ described contraction of the spleen in shock. Lewis, Werle and Wiggers²⁶ exteriorized the spleen and measured the decrease of volume in dogs put into shock by bleeding.

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20. Hausner, E.; Essex, H. E., and Mann, F. C.: *Am. J. Physiol.* **121**:387, 1938.

21. Hahn, P. F.; Bale, W. F., and Bonner, J. F., Jr.: *Am. J. Physiol.* **137**:717, 1942.

22. Keeley, J. L.; Gibson, J. G., Jr., and Pijoan, M.: *Surgery* **5**:872, 1939.

23. Searles, P. W., and Essex, H. E.: *Proc. Staff Meet., Mayo Clin.* **11**:481, 1936.

24. Essex, H. E.; Seeley, S. F.; Higgins, G. M., and Mann, F. C.: *Proc. Soc. Exper. Biol. & Med.* **35**:154, 1936.

25. Moon, V. H.: *Shock and Related Capillary Phenomena*, New York, Oxford University Press, 1938.

26. Lewis, R. N.; Werle, J. M., and Wiggers, C. J.: *Am. J. Physiol.* **138**:205, 1943.

Mylon, Winternitz, Katzenstein and de Sütö-Nagy²⁷ found that section of the spinal cord of dogs greatly reduced the hemoconcentration seen in shock induced by arterial occlusion of hindlimbs for five and one-half hours. They concluded:

. . . that any influence . . . that allows the parasympathetic nervous system to dominate results in low blood pressure and increased permeation of fluid and protein through the capillary wall. . . . The gradual fall in blood pressure that follows release of the arterial occluding tourniquet is not influenced by section of the spinal cord. On the other hand, the increase in red cell volume and loss in plasma protein is eliminated by this procedure.

They attribute the absence of hemoconcentration to interruption of the parasympathetic nervous system. However, we assumed that since the vagi were intact in their animals, the phenomenon must be due to inhibition of sympathetic motor impulses to the spleen, these being interrupted by section of the spinal cord.

The belief that the spleen plays a role in the hemoconcentration of tourniquet shock is supported by our finding that surgical removal reduced the average increase in hematocrit index in shock from 19.9 in normal animals to 4.33 mm. in splenectomized animals, and in shock following intestinal manipulation from 26.0 mm. in normal dogs to 13.4 mm. in splenectomized subjects. When the sympathetic-paralyzing drug piperidomethyl-3-benzodioxane reversed the pressor response to epinephrine to a depressor response, we observed an average increase in hematocrit index of only 9.6 mm. in tourniquet shock, as compared with 19.9 mm. in dogs receiving none of the drug.

It seems reasonable that "pharmacologic splenectomy" should be less complete than surgical extirpation. That this is true is shown by the fact that a rise of 9.6 mm. occurred in hematocrit index after infusion of piperidomethyl-3-benzodioxane, as compared with 4.33 after splenectomy. Both of these procedures abolished the rise usually seen in the first quarter of the experiment.

Casts have been applied to reduce loss of fluid into the injured limbs, a procedure also used by Katz, Shleser, Asher and Perlow²⁸ before ligating the common iliac vein. In the normal dogs, after application of tourniquets the rise in hematocrit index was only 14.8, as compared with the anticipated 19.9 mm. On the contrary, splenectomy and administration of piperidomethyl-3-benzodioxane along with casts completely abolished hemoconcentration. The sum of the increase in index in splenectomized dogs and normal dogs wearing casts is 19.1 mm., which is comparable to the 19.9 mm. increase in normal animals with tourniquet shock. This evidence suggests that local loss of fluid and contraction of the spleen account for the hemoconcentration seen in tourniquet shock in dogs.

In shock induced by loss of plasma from intestinal stripping and exposure, splenectomized animals exhibited an average rise in hematocrit index 12.6 mm. less than that of normal animals. This type of shock, due primarily to loss of plasma, resulted in a greater degree of hemoconcentration than is seen in animals with tourniquet shock. However, the spleen contributed approximately the same degree of increase in the index (12.6 mm., as compared with 14.8 mm.).

These observations suggesting that the hemoconcentration of tourniquet shock is due to splenic contraction and local loss of fluid are not supported by the studies of Cullen, Schechter, Freeman and Laws.²⁹ These authors used the

27. Mylon, F.; Winternitz, M. C.; Katzenstein, R., and de Sütö-Nagy, G. J.: *Am. J. Physiol.* **137**:280, 1942.

28. Katz, L. N.; Shleser, I. H.; Asher, R., and Perlow, S.: *Am. J. Physiol.* **137**:589, 1942.

29. Cullen, M. L.; Schechter, A. E.; Freeman, N. E., and Laws, M. K.: *Blood Substitutes and Blood Transfusion*, Springfield, Ill., Charles C Thomas, Publisher, 1942, vol. 5.

carbon monoxide method to determine changes in blood volume in traumatic shock following 1,500 blows of a rubber mallet to a limb, and they found the reduction in blood volume greater than could be accounted for by the measured loss into the injured legs in both normal and sympathectomized dogs. However, the determination of blood volume by this method depends on the degree of saturation of the red blood cells with carbon monoxide. Barcroft and Barcroft^{1a} and Hanak and Harkavy^{1c} showed that animals at rest could breathe for two hours concentrations of carbon monoxide sufficient to raise the carboxyhemoglobin in the peripheral blood to 20 per cent without its appearing in splenic blood. Splenic discharge of many erythrocytes could give evidence of apparent loss of fluid in the normal subjects. The same mechanism to a lesser degree might be noted in the sympathectomized animals, since slower and less pronounced splenic contraction was observed by Hargis and Mann^{1c} after sympathectomy. Neither section of the spinal cord²⁷ nor administration of the sympathetic-paralyzing drug piperidomethyl-3-benzodioxane in our experiments completely abolished the contribution of the spleen to the change in hematocrit index in tourniquet shock.

It is suggested that the spleen causes the rise in hematocrit index seen in dogs after injection of epinephrine and during the early stage of traumatic shock due to constriction of the dog's limbs or following intestinal stripping. Since the whole of the hemoconcentration in our animals can be accounted for by loss of fluid into the damaged limb and by splenic contraction, the concepts that generalized increased capillary permeability or systemic sequestration of plasma occurs in shock are not supported.

The question at once arises whether the spleen behaves similarly in man. In 1852 Henle³⁰ observed splenic contraction in human beings after decapitation. Paffenholz and Schürmeyer³¹ and Volicer and Vesin³² used colloidal thorium dioxide to visualize slight but definite contraction of the spleen after injection of epinephrine. If the spleen is enlarged, however, great contraction may occur (Watson³³).

The first suggestion that emotional polycythemia may occur in either human beings or animals was derived from experiments conducted on medical students in 1897. Ferrari³⁴ counted the red blood cells of a group of young men before and after an examination and found the average rise to have been 457,000 cells per cubic millimeter. Ebert and Stead³⁵ concluded that the large increases in blood volume following injection of epinephrine and exercise reported by Barcroft,³⁶ Bazett³⁷ and others³⁸ could be accounted for by inaccuracy of the carbon monoxide and dye methods of measuring blood volume. They, as well as Lucia, Aggeler, Husser and Leonard,³⁹ were unable to differentiate normal from splenectomized persons by changes in the hematocrit index following subcutaneous admin-

30. Henle, F. G. J.: *Ztschr. f. rat. Med.* **2**:229, 1852.

31. Paffenholz, W., and Schürmeyer, A.: *Klin. Wchnschr.* **10**:2076, 1931.

32. Volicer, L., and Vesin, S.: *Ztschr. f. klin. Med.* **122**:57, 1932.

33. Watson, C. J.: *Ann. Int. Med.* **12**:1782, 1939.

34. Ferrari, G. C.: *Riv. di pat. nerv.* **2**:306, 1897.

35. Ebert, R. V., and Stead, E. A.: *Am. J. M. Sc.* **201**:655, 1941.

36. Barcroft, J.; Binger, A.; Bock, A. V.; Daggart, J. H.; Forbes, H. S.; Harrop, G.; Meakins, J. C., and Redfield, A. C.: *Phil. Tr. Roy. Soc., London, s.B* **211**:419, 1922.

37. Bazett, H. C.; Sunderman, F. W.; Doupe, J., and Scott, J. C.: *Am. J. Physiol.* **129**:69, 1940.

38. Ludwig, H.: *Ztschr. f. d. ges. exper. Med.* **80**:36, 1931. Wollheim, E.: *Ztschr. f. klin. Med.* **116**:269, 1931.

39. Lucia, S. P.; Aggeler, P. M.; Husser, G. D., and Leonard, M. D.: *Proc. Soc. Exper. Biol. & Med.* **36**:582, 1937.

istration of 1 mg. of epinephrine hydrochloride. Nor could Dill, Talbott and Edwards⁴⁰ find any difference among normal and splenectomized persons following exercise.

In our 6 normal subjects there was an average rise in hematocrit index of 3.4 mm., as compared with a 1.1 mm. change in splenectomized subjects, after intravenous injection of 2 mg. of epinephrine hydrochloride. This is small compared with the 10.5 mm. change seen in our dogs, but it is constant and probably of some significance. The fact that a rise occurred in our experiments and not in others is doubtless due to the use of 2 mg. of epinephrine hydrochloride intravenously as compared with 1 mg. subcutaneously.

On the basis of this evidence it seems that the human spleen contributes much less to the rise in hematocrit index seen in shock than do the spleens of dogs. However, final judgment must be reserved until more is known of human splenic blood volume, and whether the spleen contains highly cellular blood and whether it contracts actively.⁴¹

SUMMARY AND CONCLUSIONS

Approximately 65 per cent of the rise in hematocrit index in dogs in tourniquet shock and 50 per cent of that in shock induced by intestinal manipulation can be accounted for by splenic contraction and discharge of highly cellular blood from the spleen.

The splenic contribution to changes in the hematocrit index occurs during the first one to two hours of the experiment.

This portion of erythremia can be eliminated by splenectomy and partially so by infusion of piperidomethyl-3-benzodioxane. Both procedures prevent the early, sharp rise of the hematocrit index seen in traumatic shock.

Thirty-five per cent of the rise in hematocrit index in tourniquet shock can be prevented by applying plaster casts to the hindlimbs. Practically all increase can be eliminated with casts applied to the traumatized limbs combined with either infusion of piperidomethyl-3-benzodioxane or splenectomy.

Since hemoconcentration in the types of shock under investigation can be accounted for by local loss of plasma at the site of injury and splenic participation, the concept of generalized increase in capillary permeability is not supported.

Epinephrine produced a slight rise in the hematocrit index in 6 normal persons but not in 6 splenectomized persons. The rise was one third of that seen in dogs. It appears that splenic participation may not be as significant in traumatic shock of human beings as in that of animals.

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40. Dill, D. B.; Talbott, J. H., and Edwards, H. T.: *J. Physiol.* **69**:267, 1930.

41. Since this manuscript was submitted, C. J. Watson and J. R. Paine (*Am. J. M. Sc.* **205**:493, 1943) have reported observations made on 9 patients during splenectomy. They found that epinephrine caused marked splenic contraction and an associated systemic erythremia due to discharge of cellular splenic blood. This report obviates the need for studies we had in progress.

ANGIOFIBROMA OF THE ILEUM

CLINICAL PICTURE IN TUMORS OF THE SMALL INTESTINE

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Benign tumors of the small intestine are not common (tables 1 and 2). They are seldom recognized before operation or autopsy.

Since the first comprehensive review of benign tumors of the small intestine was published in 1899 by Hertaux,¹ there have been few extensive contributions to the subject. In 1917, King² compiled abstracts of 118 cases of benign tumor recorded in the literature and gave a complete report of 1 case of sessile submucous

TABLE 1.—*Comparative Incidence of Tumors of the Stomach, Small Intestine and Large Intestine*

Author	Material	Location	Benign	Malignant	Total
Raiford ⁴	Autopsies, 11,500	Stomach.....	58	453	511
		Small intestine.....	33	38	71
	Surgical specimens, 45,000	Colon.....	87	281	368
			178	772	950
Merchant ⁸	Autopsies, 7,340	Stomach.....	43		
		Small intestine.....	24		
	Surgical specimens, 50,775	Colon.....	177		
			244		

TABLE 2.—*Comparative Incidence of Benign and Malignant Tumors of the Small Intestine*

Author	Benign	Malignant	Total
Raiford ⁴	33	38	71
Hartman [*]	44	97	141

* Hartman, H. R.: Lesions of Small Bowel Other Than Peptic Ulcer, M. Clin. North America 19:365, 1935.

fibroma of the jejunum. Brown,³ in 1924, reported an instance of cavernous hemangioma of the jejunum and reviewed the literature on vascular tumors of the intestines. In 1932, Raiford⁴ published a thorough discussion of tumors of the small intestine. He found 33 benign tumors of the small intestine⁵ described in all available records at the Johns Hopkins Hospital; the material reviewed included 11,500 general autopsies and 45,000 general surgical specimens. The complete records of the Mayo Clinic up to 1933 were reviewed by Rankin and

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1. Hertaux: Note sur les tumeurs benignes de l'intestin, Arch. prov. de chir. 8:701, 1899; 9:1, 1900.

2. King, E. L.: Benign Tumors of the Intestine, Surg., Gynec. & Obst. 25:54, 1917.

3. Brown, A. J.: Vascular Tumors of the Intestine, Surg., Gynec. & Obst. 39:191, 1924.

4. Raiford, T. S.: Tumors of the Small Intestine, Arch. Surg. 25:122 (July) 1932.

5. This figure does not include carcinoids, ectopic pancreatic tissue and cysts.

Newell.⁶ They summarized 35 cases of benign tumor of the small intestine, 11 of which had been previously reported. Kirshbaum⁷ reviewed the 5,754 autopsies at the Cook County Hospital from 1929 to 1935 and found 12 cases of benign tumor of the small intestine. Merchant⁸ summarized the records of the Royal Victoria Hospital of Montreal from 1915 to 1939 and found 6 benign tumors among 50,775 surgical specimens and 18 reported in 7,340 autopsies. The greater incidence of these tumors in autopsy material as contrasted with surgical material is due in part to the fact that some are undiagnosed clinically and in part to the fact that many are merely observed incidentally at autopsy.

There have been other reports of single cases in which no unusual features were presented.

A benign tumor of the small intestine may arise from any of the components of the wall. Table 3 gives a summary of the place of occurrence and the nature of the tumors reported by several authors. It shows that they were more frequent in the ileum than in the jejunum or duodenum. Of interest is the occurrence of neurofibroma as indicated by Grill and Kuzma,⁹ either with or without von Recklinghausen's neurofibromatosis. There have been 5 cases of nerve sheath tumor (neurilemmoma) of the small intestine reported,¹⁰ in 2 of which the growth

TABLE 3—Location and Character of Benign Tumors of the Small Intestine*

Type	Duodenum	Jejunum	Ileum	Unspecified	Total
Fibroma	2	4	10	1	17
Fibroadenoma...	1	1
Myoma and fibromyoma	8	10	15	4	37
Adenoma	10	8	14	..	32
Angioma	3	2	1	1	7
Lipoma..	4	2	7	4	17
Neurofibroma	1	3	4
Osteochondroma	1	1
Total	29	26	47	14	116

* Compiled from papers by King,² Raiford,⁴ and Rankin and Newell.⁶

was in the duodenum and in 3 in the jejunum or ileum. This type of tumor is encountered in the stomach much more frequently than in the intestine. Rarely, a congenital lesion is found, such as the hemangioendothelioma in the case reported by Blahd, Maschke and Karsner.¹¹

The direction of enlargement of a tumor depends on whether it arises on the luminal side or on the extraluminal side of the muscular layer. Thus, a fibroma arising in the submucosa projects into the lumen of the canal, while one in the subserosa projects into the peritoneal cavity. A myoma which arises from the muscular layer may project in either direction.

6. Rankin, F. W., and Newell, C. E.: Benign Tumors of the Small Intestine. Report of Twenty-Four Cases, Surg., Gynec. & Obst. **57**:501, 1933

7. Kirshbaum, J. D.: Submucous Lipomas of the Intestinal Tract as a Cause of Intestinal Obstruction, Ann. Surg. **101**:734, 1935

8. Merchant, F. T.: Intussusception Due to Hemangioma of the Jejunum, Arch. Surg. **39**:1031 (Dec.) 1939.

9. Grill, J., and Kuzma, J. F.: Recklinghausen's Disease with Unusual Symptoms from Intestinal Neurofibroma, Arch. Path. **34**:902 (Nov.) 1942

10. Stout, A. P.: The Peripheral Manifestations of the Specific Nerve Sheath Tumor (Neurilemmoma), Am. J. Cancer **24**:751, 1935

11. Blahd, M. E.; Maschke, A. S., and Karsner, H. T.: A Case of Hemangio-Endothelioma of the Ileum, Am. J. Dis. Child **26**:379 (Oct.) 1923

The development of the extraluminal type of tumor is insignificant when contrasted with that of the intraluminal type. As the latter projects into the lumen, it may be sessile at first. In most instances the peristaltic activity exerts sufficient force to move the mass away from its point of origin, so that a pedicle is formed. With pedunculated tumors, complications are much more frequent than with other forms.

There are four complications which may occur with a pedunculated tumor of the small intestine: (1) necrosis of the tumor mass; (2) bleeding from an eroded surface; (3) partial or complete obstruction of the lumen, and (4) intussusception. These may coexist in the same person. Necrosis occurs because of paucity of circulation through an attenuated pedicle. Fever and persistent occult blood in the stools may result from necrosis or from erosion. Partial obstruction due to a tumor is identical with that from any other cause. There are hypertrophy of the tunica muscularis and dilatation of the lumen above the obstruction, while below it the intestinal wall is unchanged and the lumen small. Complete obstruction results from intussusception of the tumor-bearing segment into the subadjacent portion of bowel or may be due to encroachment of the tumor on the lumen or impaction of intestinal contents against it. In this condition, the lumen above the obstruction is dilated and the walls are thin and tense.

Chronic, intermittent or acute intestinal obstruction is suggested by the history. Recurrent attacks of acute abdominal pain with intervals free from pain are common. The attacks of pain tend to become more severe with each recurrence. Nausea and vomiting are frequent during the attacks, being intense if the tumor is high in the small intestine.

The intermittent colicky pain repeatedly starts in the same area and tends to remain localized. Owing to the frequent location of the tumor in the ileum, the pain is often in the right lower quadrant of the abdomen; hence, differentiation from appendicitis is necessary. These attacks of pain associated with nausea and often with vomiting end suddenly, and the patient feels well until the next attack.

Constipation is a frequent complaint. It is usually marked between the episodes of obstruction and complete during them.

Physical symptoms are few if there are no complications. There may be evidence of a recent loss of weight; this is more often apparent with a malignant tumor. As with other forms of mechanical obstruction, there is often a region of localized tenderness in the abdomen, and sometimes a mass can be palpated.

Examination of the stools sometimes reveals frank or occult blood. This is especially frequent if the growth is a cavernous hemangioma. Any type of benign tumor in the duodenum is likely to produce considerable hemorrhage. Balfour and Henderson¹² emphasized this in a review of 6 benign tumors of the duodenum (2 myomas, 2 adenomas, 1 adenomatous polyp and 1 hemangioma). They stated: "The most significant sign was hemorrhage, which was severe in 4 of the 6 cases."

After one or more of the attacks of obstruction, a symptom-free interval may be ended by acute intussusception. There is a sudden onset of severe pain, and it is localized to a definite area. Palpation frequently reveals an elongated sausage-shaped abdominal mass. Vomiting and abdominal distention occur, and bloody stools may be passed.

12. Balfour, D. C., and Henderson, E. F.: Benign Tumors of the Duodenum, *Ann. Surg.* 89:30, 1929.

The use of the roentgen rays in the diagnosis of tumors of the small intestine is seldom discussed in the literature. Kiefer¹³ stated that the roentgen examination may be disappointing except when carried out either during or just after a period of obstruction. At such a time, a flat plate roentgenogram may reveal the distended loops of small intestine in "stepladder" arrangement. Fluid levels may be present in the distended loops. The administration of barium sulfate by mouth is contraindicated in the presence of acute intestinal obstruction; when there has been chronic obstruction or repeated episodes of complete obstruction have occurred, it should be used only with full realization that it can precipitate acute obstruction.

REPORT OF A CASE

A 68 year old white woman was admitted to the Norwegian-American Hospital on April 8, 1940, complaining of vague intermittent abdominal cramps of four months' duration. These had often been associated with attacks of nausea in the preceding two months. For three



Fig. 1.—Roentgenogram taken after a barium sulfate meal. The arrow indicates the filling defect interpreted as a probable tumor of the ileum.

weeks there had been occasional vomiting accompanying the cramps and nausea. Blood had not been noted in the vomitus, nor had the stools been tarry. She had had a poor appetite and had been constipated since the onset of symptoms. Before her admission to the hospital, she had had a barium sulfate meal. This revealed a filling defect in the ileum, which was interpreted as probable tumor of the small intestine (fig. 1).

The patient was an elderly, well developed, fairly well nourished woman who was not acutely ill. The blood pressure was 168 systolic and 94 diastolic; the pulse rate was 88 and the respiratory rate 24 per minute, and the temperature was 99.4 F. The abdomen was distended; no organs or masses were palpable, but there was slight tenderness on the right side of the umbilicus. There were no other unusual findings. The erythrocyte count was 3,600,000, the hemoglobin content 12 Gm. and the leukocyte count 9,700. The urine contained albumin (3 plus) and occasional casts. The report on a flat plate roentgenogram of the abdomen was "considerable gas throughout the upper portion of the small intestine."

It was believed that there was obstruction of the small intestine, and preparations for operation were instituted. These consisted of hydration and the supplying of iron, minerals and

13. Kiefer, E. D.: Clinical Aspects of Chronic Disorders of the Small Intestine, *J. A. M. A.* **113**:1546 (Oct. 21) 1939.

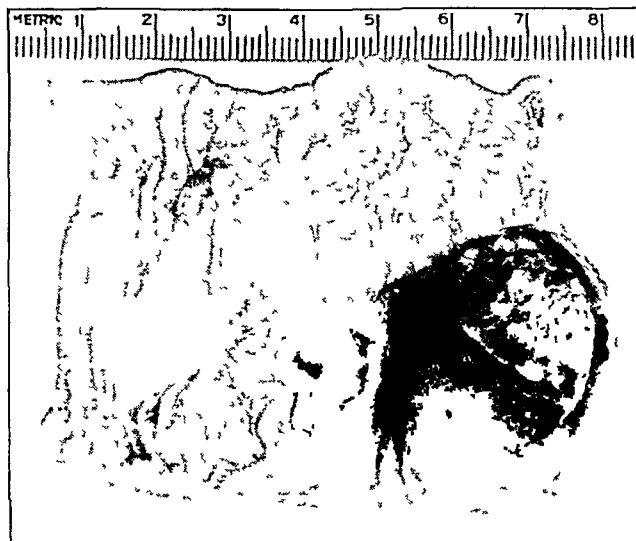


Fig. 2—Pedunculated angiofibroma of the ileum. The intussusceptions were reduced before the resection was done.

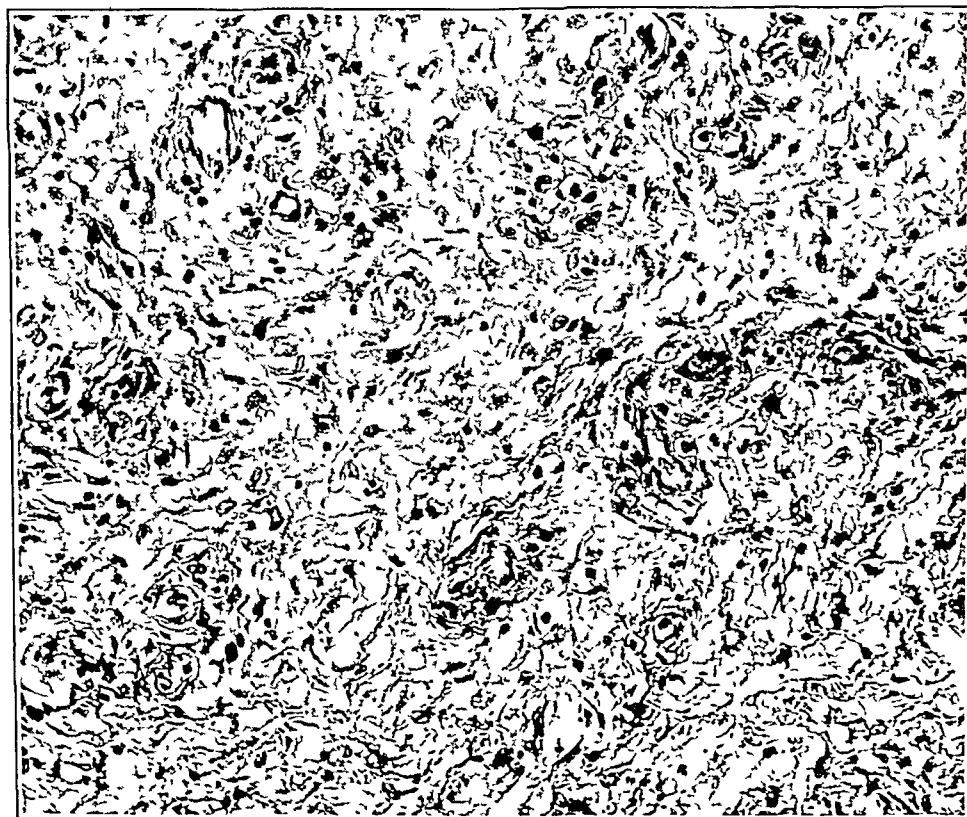


Fig. 3—Angiofibroma of the ileum ($\times 100$) There are numerous vascular spaces lined by flat endothelial cells

vitamins. A high caloric liquid diet was allowed. Intermittent intestinal suction, with use of a Miller-Abbot tube, was also employed, in order to secure and maintain decompression of the intestine above the obstruction. During this period of preparation, the temperature reached 99.4 F. on several occasions.

On April 13, the abdomen was opened, and a double intussusception was found in the ileum. This was an invaginated section of ileum with a pedunculated tumor near its tip, and the entire intussusception and tumor had subsequently invaginated into the next lower segment of ileum (fig. 2). The lumen above the obstruction was dilated and the wall thickened. The intussusceptions were reduced, and 8 cm. of intestine, including the tumor, was resected. Primary end to end anastomosis was done. The convalescence was uneventful, and the patient was discharged on the eleventh postoperative day. After the third postoperative day, the temperature did not rise above 98.6 F.

Pathologic Report (Dr. H. R. Fishback).—Gross Observations: The specimen consisted of a segment of bowel 7 cm. in length, the wall of which appeared unchanged. Near one end of the segment there projected from the mucosa into the lumen a pedunculated tumor mass 4 cm. in length and 2.5 cm. in diameter. The proximal end of this was grayish pink and had a smooth mucosal covering. The distal half was dark bluish red and had an eroded surface. On section the tissue had a central pinkish white fibrous core. Around this, beneath the covering of the mucosa, was a slightly softer zone 5 mm. thick, which was pinkish yellow.

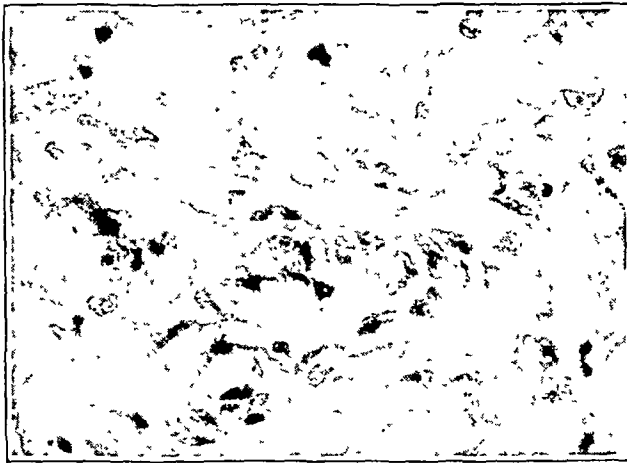


Fig. 4.—Angiofibroma of the ileum ($\times 200$). The vascular spaces are surrounded by fibroblasts and strands of collagen.

Microscopic Observations (figs. 3 and 4): Sections showed a structure made up of white fibrous connective tissue. This was intimately interlaced between innumerable small capillary blood vessels. In places these had well defined walls, but in others the walls were largely endothelial cells and many of the capillaries appeared collapsed. Here and there were diffuse small streaks of hyalinization. Part of the tumor was covered over by intestinal mucosa, somewhat engorged and containing inflammatory cells, and it showed a layer of muscularis mucosae. A portion was ulcerated, with a covering of fibrin mingled with red cells and leukocytes. Beneath this was an area of chronic inflammatory reaction of nonspecific type.

Diagnosis: The diagnosis was angiofibroma of the intestine.

Subsequent Course.—Fourteen months after the operation, a report was received from the patient's daughter in which it was stated that within four months after the removal of this tumor there had been a gain of weight of 24 pounds (11 Kg.). The patient had had a good appetite, and there had been no further constipation.

COMMENT

Double intussusception resulting from a tumor of the small intestine was reported by James Nicoll in 1899. This was in a woman of 23 years who was seen with pain, persistent vomiting and constipation. She had had a similar attack two weeks before, but it had been milder; in the intervening two weeks

pain after meals had been frequent, lasting about an hour each time. At operation, a double intussusception was found. A portion of intestine 5 feet (1.5 meters) long was resected, and in the lumen, "just above the intussusception, was a tumor about the size of a pigeon's egg." End to end anastomosis was done, and the patient recovered. The tumor was a typical cavernous hemangioma.

Vague, intermittent abdominal cramps, sometimes associated with nausea and vomiting, should lead to consideration of partial obstruction of the intestine. Constipation of marked degree is also a part of this picture. When such a history is climaxed by an acute intussusception (signs of complete obstruction plus a palpable abdominal mass), the presence of a pedunculated tumor of the small intestine is highly probable.

The sequence of intestinal obstruction followed by a symptom-free period recurring at variable intervals results from local spasm of the intestine in the vicinity of the tumor or from partial invagination. Sudden relief follows relaxation of the former or reduction of the latter.

Anemia in this patient was due to her diminished appetite and limited retention of food resulting from the chronic partial intestinal obstruction. These factors also explain her constipation. The low grade fever occasionally present before operation may be explained by the presence of necrosis at the tip of the tumor, from which protein products could enter the blood stream. After the operation this fever did not recur. Albuminuria was caused by an unrelated chronic glomerulonephritis.

The complete absence of symptoms for fourteen months after the operation attests the importance of diagnosis and surgical therapy for benign tumors of the small intestine.

The microscopic structure of this tumor was one of many capillary vessels and capillary buds in a bed of fibrous connective tissue. Many of the vessels were merely endothelium-lined spaces surrounded by connective tissue, without other evidence of a wall. This structure closely fits the characteristic picture of angiofibroma as described by Ewing.¹⁴ Angiofibroma may arise from the vascular elements of any part of the body; although growths of this type have been reported in many organs, none has been reported previously in the small intestine.

SUMMARY

The literature on benign tumors of the small intestine is briefly reviewed.

There are two directions in which such a tumor may expand: toward the peritoneal cavity (extraluminal) and toward the lumen of the intestine (intraluminal). Growth in the former direction rarely results in complications, while intraluminal expansion is frequently associated with necrosis, bleeding, intestinal obstruction and intussusception.

Diagnosis is made from a history of recurrent attacks of colicky pain associated with nausea and vomiting plus marked constipation. Finally, intussusception may occur, with acute obstruction and a palpable abdominal mass. This sequence is probable evidence of a pedunculated tumor of the small intestine.

Surgical operation is usually wholly successful.

A case of angiofibroma of the ileum with a double intussusception is presented. There are no previous reports of angiofibroma of the intestine.

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14. Ewing, J.: *Neoplastic Diseases*, ed. 4, Philadelphia, W. B. Saunders Company, 1942.

CHRONIC EFFECTS RESULTING FROM DOWNWARD TRACTION ON THE LIVER

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I have described experiments in which circulatory failure was produced by maintaining a constant traction on the liver.¹ One is ordinarily prone, however, to think only of the acute effects of circulatory failure (hemoconcentration, loss of fluid, low blood pressure, rapid and thready pulse, etc.), without at the same time thinking of the chronic effects which may come after an animal has been subjected to periods of reduction of blood pressure, not to shock but to "preshock" levels. In this connection these questions present themselves: 1. What damage is done to the animal during relatively short periods of low blood pressure (50 to 60 minutes)? 2. If any damage occurs, is it reparable or irreparable? 3. What is the mechanism of the damage?

The purpose of this paper, therefore, is to present the results and interpretations of a number of experiments designed to produce chronic effects. Traction was exerted on the livers of dogs for short periods, and the animals were allowed to recover for observation.

METHODS OF PROCEDURE

A number of observations were made on the animals before and after operation. These observations included: general condition of the animal, water metabolism, urea content of the blood and urine, results of qualitative urinalysis, serum proteins, renal function (determined by urea clearance and dye tests), blood pressure and electrocardiographic characteristics. The observations made in the normal, or preoperative, period constituted control experiments for each animal used. This control, or normal, period of observation was usually ten days to two weeks.

At the beginning of the experiments to be reported here an attempt was made to apply traction for approximately the same period (about two hours) as was necessary to produce the beginning effects of circulatory failure in the experiments designed to produce acute effects. It was found, however, that many animals so treated failed to recover for sufficient time to allow desirable observations; hence a period was found for which traction could be kept on the liver and complete recovery obtained. This period ranged from fifty to sixty minutes.

The animals were operated on under anesthesia induced with soluble pentobarbital U. S. P. (pentobarbital sodium). Aseptic care was taken in all cases. After the incision was made the liver was pulled away from its approximation with the diaphragm and large pieces of sterile gauze were placed over it to prevent direct damage by the brass "hand" which was used to exert traction. The "hand" was then placed over the gauze-protected liver, and traction was exerted for fifty to sixty minutes continuously by tying the "hand" to the opposite end of the operating table. During this period the abdomen was covered with sterile towels, and at the end the "hand" was removed and the incision was closed.

CHEMISTRY OF BLOOD AND OF URINE

Urea.—Five cubic centimeter samples of blood were drawn two to three times a week in preoperative periods and daily after the operation for three weeks. Filtrates were prepared by sodium tungstate-sulfuric acid precipitation, and 5 cc. samples of the filtrate were used to

Aided by grants from the Julius Rosenwald Fund and the State of Texas.

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A part of a dissertation submitted to the Division of Biological Sciences, Department of Physiology, the University of Chicago, in candidacy for the Ph.D. degree, September, 1942.

1. Booker, W. M.: *Anesth. & Analg.* **20**:237, 1941; **22**:93, 1943.

determine urea by the well known Van Slyke method. Urine was prepared by dilution (1 to 50 cc.) and filtration, after which 5 cc. samples of the filtrate were used to determine urea by the same method used for blood urea.

Serum Proteins.—Five cubic centimeter samples of blood were drawn at the same intervals as just described and allowed to clot, and after they had been centrifuged the serum was removed. One cubic centimeter samples of serum were used to determine the protein nitrogen by the Pragli steam distillation modification of the micro-Kjeldahl method.

Urinalysis.—Urine was tested for the presence of albumin by the Heller nitric acid ring test and was tested for bile pigments by the Gmelin nitric acid test.

TESTS OF RENAL FUNCTION

These tests were performed on female dogs, on which perineostomy had been performed in order to make the urethra easily accessible. The animals were trained to lie still during the tests, which required from one to two hours after the injection of 1 cc. of phenolsulfonphthalein. The same period was used for collection of blood and urine for urea clearance studies.

ARTERIAL BLOOD PRESSURE

Normal, or control, pressures were taken approximately twice a week for two to three weeks before operation. The animals were easily trained for manipulation of the needle into the artery

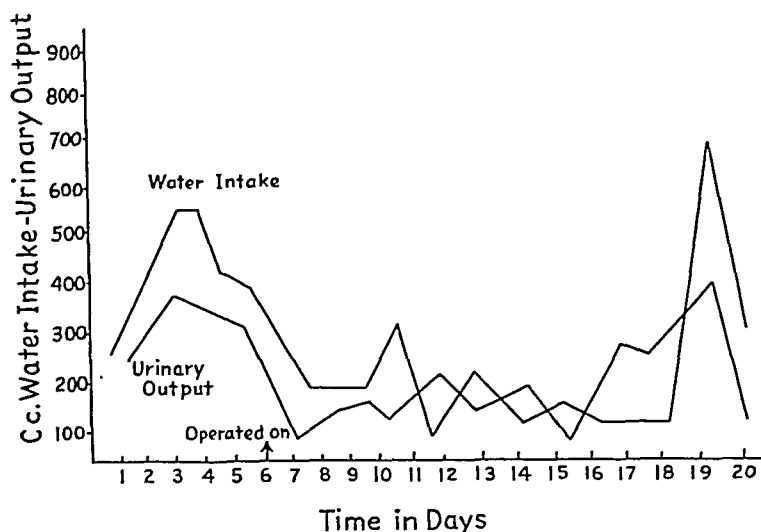


Fig. 1.—A typical experiment showing the water metabolism of an animal before and after traction on the liver.

(femoral), and after a few times little or no movement occurred when the needle was inserted. In the early postoperative weeks pressures were taken twice a week. Later they were taken once a week.

ELECTROCARDIOGRAPHIC STUDIES

Electrocardiographic records were taken several times before operation and at various postoperative intervals (once to twice a week). It was thought advisable, in view of the mobile character of the dog's heart, to change the positions of the animal on the table in preoperative tests (as control experiments) to see if rotation of the heart could possibly account for the changes in the contours of the records postoperatively. Records were taken (1) with the animal on its right side and the legs extended at right angles to the longitudinal axis of the body; (2) with the animal rotated slightly to the right and the feet extended upward; (3) with the animal flat on its back and the feet extended upward and in a few instances (4) with the animal on its left side.

INTERPRETATIONS AND RESULTS

During the first two or three postoperative days animals always showed depression and inactivity, a reduction or sometimes a complete loss of appetite and, of course, a loss of weight. Equally striking was the suppression of secretion of urine,

followed in time by pronounced diuresis (fig. 1). Later there were periods in which the output of urine again fell to 5 to 10 cc. a day and the urine was heavy with bile pigments. Such periods recurred about every three weeks.

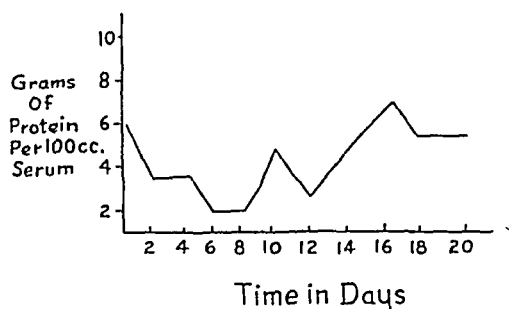


Fig. 2.—A typical experiment showing the changes in the serum proteins following traction on the liver. Preoperative or control values ranged between 6.0 and 6.5 Gm. per 100 cubic centimeters.

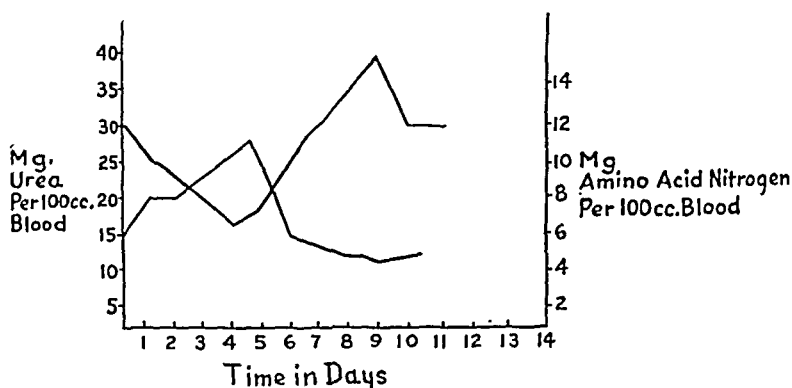


Fig. 3.—A typical experiment showing the changes in blood urea and blood amino acids following traction on the liver. Preoperative or control blood urea values ranged from 30.0 to 35.0 mg. per hundred cubic centimeters. Preoperative blood amino acid values ranged between 4 to 6 mg. per hundred cubic centimeters.

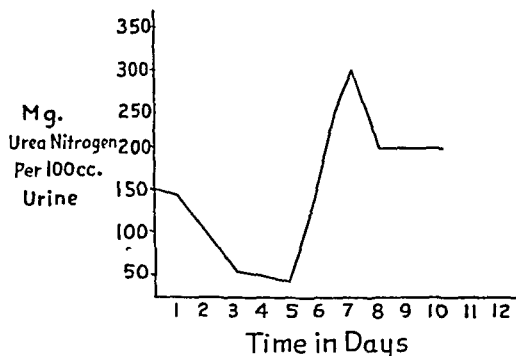


Fig. 4.—A typical experiment showing the changes in urinary urea following traction on the liver.

SERUM PROTEINS

The sharpest changes in the serum proteins occurred the first postoperative week, as can be seen in figure 2. The urine in this and subsequent weeks was positive for albumin, and this would seem to indicate that damage was done to the

kidneys during the period of traction on the liver. It seems safe to say that the fall in the serum proteins can be accounted for by the route of the kidney. The loss of albumin was not spasmodic; rather there was a daily loss. It therefore seems amazing that there was a return of the serum proteins to preoperative or even higher levels after two weeks. It is probable that the recovery of the liver from temporary functional damage (to be discussed hereinafter) made possible a high output of plasma proteins after a week, sufficient to cope with the loss of albumin from the kidney and perhaps in the peritoneal cavity.

BLOOD AND URINARY UREA AND AMINO ACIDS

It was suspected that in view of definite suppression of secretion of urine there might be damage to the kidneys adequate to cause retention of urea. Surprisingly, however, the blood urea did not increase but decreased, as did also the urinary urea (figs. 3 and 4). In view of the work of Bollman and Mann² and later of Mann,³ clearly pointing out the liver as the source of urea formation, it was thought that perhaps the liver was functionally damaged during traction and that there might be, as a result, reduction in urea formation. To prove this, attention was turned to the blood amino acids. Figure 3 shows that the increase in amino acids is concomitant with the decrease in blood urea; when the concentration of urea rises that of amino acids falls.

DYE AND UREA CLEARANCE TESTS

These tests failed to show significant differences between the function of the kidney postoperatively and its function preoperatively. In all cases dye appeared in the urine in about six minutes after it was injected and after an hour normal percentages of dye had been excreted. It must be remembered that there is considerable reduction in urea formation during the first postoperative week, and in this period particularly the urea clearance test is not reliable. In a general way the results of the clearance tests in these experiments are in agreement with the work of Corcoran and Page⁴ and of other investigators who were unable to note distinct changes in the results of clearance tests unless the blood supply to the kidney was almost shut off by the arterial clamp.

It is interesting, in the matter of damage to the kidney, that Penner and Bernheim⁵ in 1940 described bilateral cortical changes in the kidney in patients who had come to autopsy and whose histories showed they had experienced periods of low blood pressure or even shock. Penner and Bernheim were able to reproduce these changes in dogs experimentally by subjecting them to periods of low blood pressure. They expressed the opinion that the alterations were due to reflex vasoconstriction sufficient to produce ischemic necrosis of the kidney. During the studies now being reported, histologic examination of sections from the kidney revealed mild but definite damage, reflected in fatty degeneration of the tubular cells and thickening of Bowman's capsule (fig. 5).

2. Bollman, J. L., and Mann, F. C.: *Am. J. Physiol.* **92**:92, 1930.

3. Mann, F. C.: *The Liver and Medical Progress*, J. A. M. A. **117**:1577 (Nov. 8) 1941.

4. Corcoran, A. C., and Page, I. H.: (a) *Am. J. Physiol.* **126**:354, 1939; (b) *J. Lab. & Clin. Med.* **26**:1713, 1941.

5. Penner, A., and Bernheim, A. I.: *Acute Ischemic Necrosis of the Kidney*, *Arch. Path.* **30**:465 (Aug.) 1940.

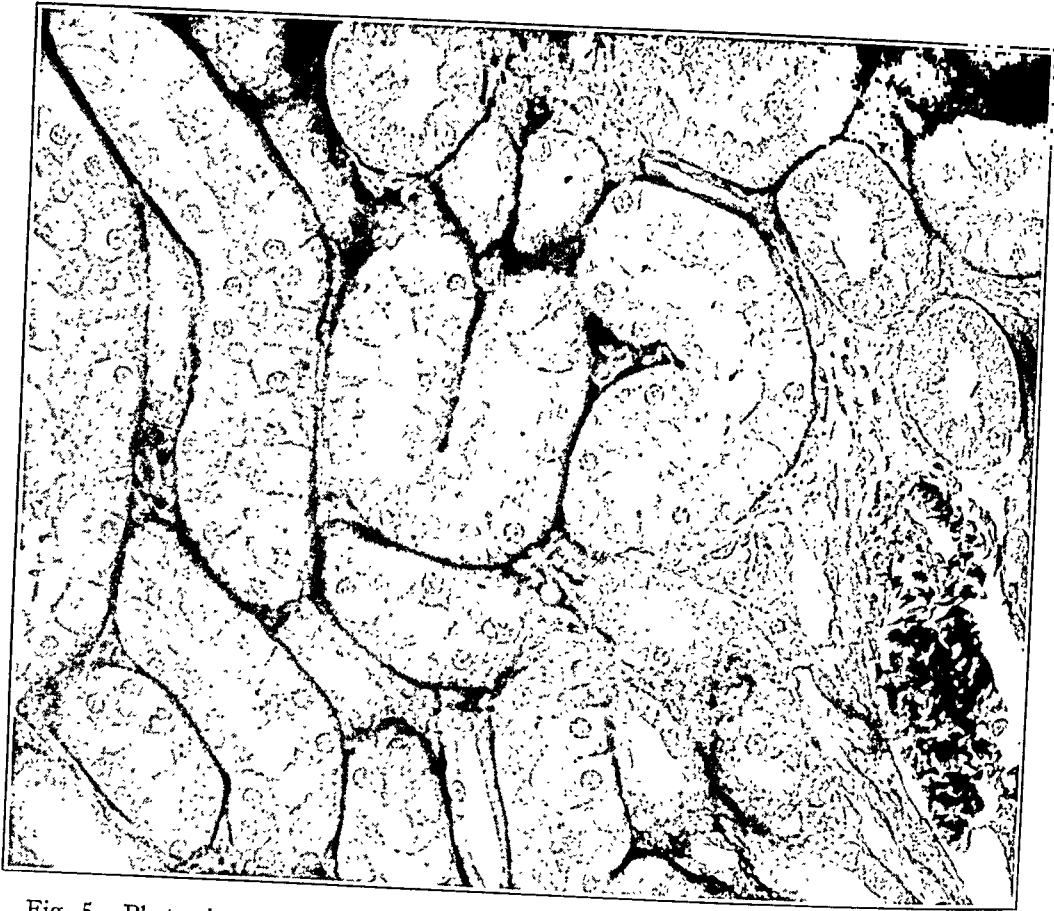


Fig. 5.—Photomicrograph of a histologic section of a kidney removed from an experimental animal brought to autopsy. Traction had been exerted on the liver several months before the section was made. Note the degeneration of the tubular epithelium. Free-hand sections removed from this kidney stained positive for fat in sudan III. $\times 400$.

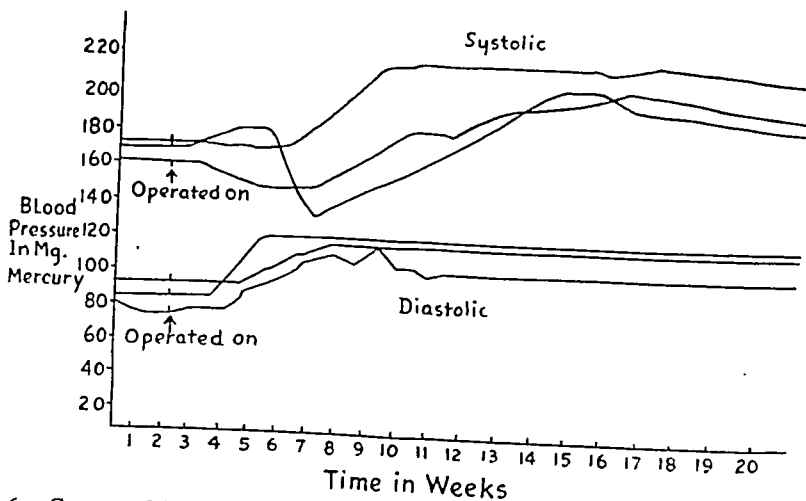


Fig. 6.—Course of blood pressure in 3 animals, as representative of the course in 7 animals, following traction on the liver. The first two weeks were control periods. Pressures were taken on the Hamilton manometer.

HYPERTENSION

Stimulated by the classic work of Goldblatt and his co-workers⁶ and by that of Page and Corcoran and many others, I decided to follow the course of blood pressure in a number of animals to determine if renal hypertension could be demonstrated as a result of damage to the kidney during traction on the liver. It will be noticed in figure 6 that significant rises in both systolic and diastolic blood pressure can be seen.

Recently Corcoran and Page^{4b} made important contributions to the subject of hypertension of renal origin. They expressed the opinion that in the "Goldblatt kidney" there is a reduction of pulse pressure and not of blood flow, unless the clamp is made very tight, and that reduction of pulse pressure is the chief cause of damage to the kidney in such cases. They pointed out that "organs perfused in the absence of pulsatile flow become edematous and their cells may lose their normal permeabilities to vital dyes." The mechanism of the damage is by no means clear, but it is sufficient to cause the release of a pressor substance which subsequently accounts for the maintained hypertension. It seems important from the point of view of the present work that from reduction either of blood flow or of pulse pres-

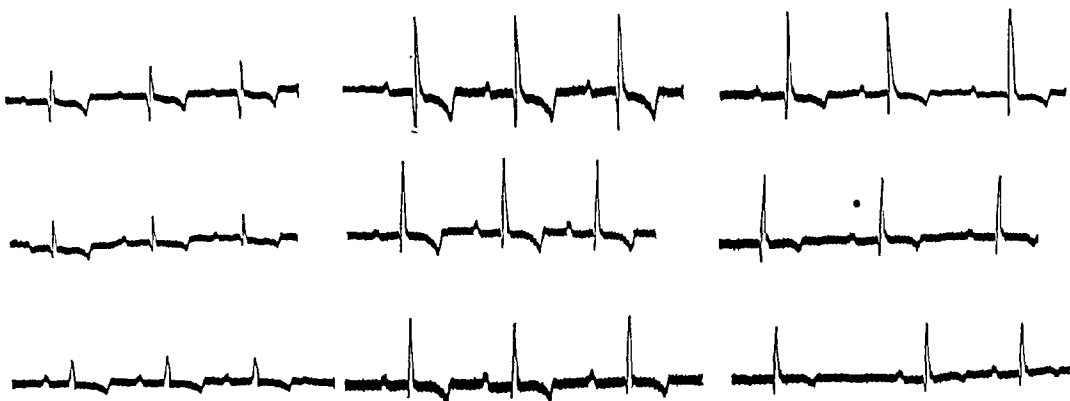


Fig. 7.—A typical experiment showing the effect of changes in position of the animal on the contours of the electrocardiograms. This control experiment was designed to obviate the possibility that changes in position of the heart might account for the changes in the contours of the electrocardiograms after traction on the liver.

sure there is established in the kidney during the brief period of low arterial and high venous pressure an anoxic condition adequate to cause renal damage and release of a pressor substance.

At least two ideas of pressor mechanisms have been advanced: 1. Corcoran and Page^{4b} postulated that renin, formed as a result of damage to the kidney, is acted on by a renin activator, producing angiotonin—itsself the pressor substance. Interestingly, a counteraction may take place, in which a renin inhibitor is relased by undamaged cells and prevents the liberation and pressor action of angiotonin. Furthermore, repeated injections of renin or angiotonin result in failure of the blood pressure to rise because of the formation of the renin inhibitor—producing what is called tachyphylaxis. 2. Houssay⁷ and Braun-Menendez, Fasciola, Leloir and Muñoz,⁸ on the other hand, described a different sort of humoral mechanism. They

6. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: *Am. J. Path.* 9:942, 1933.

7. Houssay, B. A.: *Medicina*, Buenos Aires 1:167, 1941.

8. Braun-Menendez, E.; Fasciola, J. C.; Leloir, L., and Muñoz, J. M.: *Rev. Soc. argent. de biol.* 15:420, 1939.

expressed the opinion that renin (itself not vasoactive) is liberated from damaged kidneys and acts on a pseudoglobulin, "hypertensinogen" to produce "hypertensine," which is vasoactive. They described an inhibitory substance, "hypertensinase," which prevents the action of "hypertensine." In essence these two theories of humoral mechanism agree, although a different terminology is employed.

It is, however, beyond the scope of this paper to enter into full discussion of the case for the humoral mechanisms in the cause of hypertension. It seems clear that some substance is liberated from a damaged kidney, or perhaps from certain cells of a damaged kidney, which causes a maintained vasoconstriction. In these



Fig. 8.—A typical experiment comparing the cardiac effects of traction on the liver on unatropinized animals with similar effects on those treated with atropine.

experiments, the important question is: Why must two or three weeks elapse before there are significant rises in blood pressure? There seem to be two possibilities:

1. The undamaged cells of a kidney are liberating an inhibitor substance which is able to prevent for a while the rise in blood pressure. This might find support in the results of the experiments of Goldblatt and his associates, in that the tighter the clamp the greater the damage and the faster and higher the rise in blood pressure.
2. Recently Page, McSwain; Knapp, and Andrus^{8a} have shown that the renin

8a. Page, I. H.; McSwain, B.; Knapp, G. M., and Andrus, W. deW.: *Am. J. Physiol.* 135:214, 1941.

activator probably comes from the liver and in animals with a damaged liver or in hepatectomized animals there is failure of the blood pressure to rise following clamping of the renal artery. In this paper it has been established that there is perhaps a temporary functional damage of the liver lasting at least a week, and it does not seem far fetched, therefore, to postulate the view that the slow rise in blood pressure may be due to failure of the liver to liberate the renin activator during damage.

THE HEART

In early experiments it was observed in an animal at autopsy that there was an unusual hardness at the tip of the left ventricle, which on histologic examination revealed what was described as nuclear degeneration and necrosis. Later by crude auscultation it was revealed that animals always had slow and extremely arrhythmic

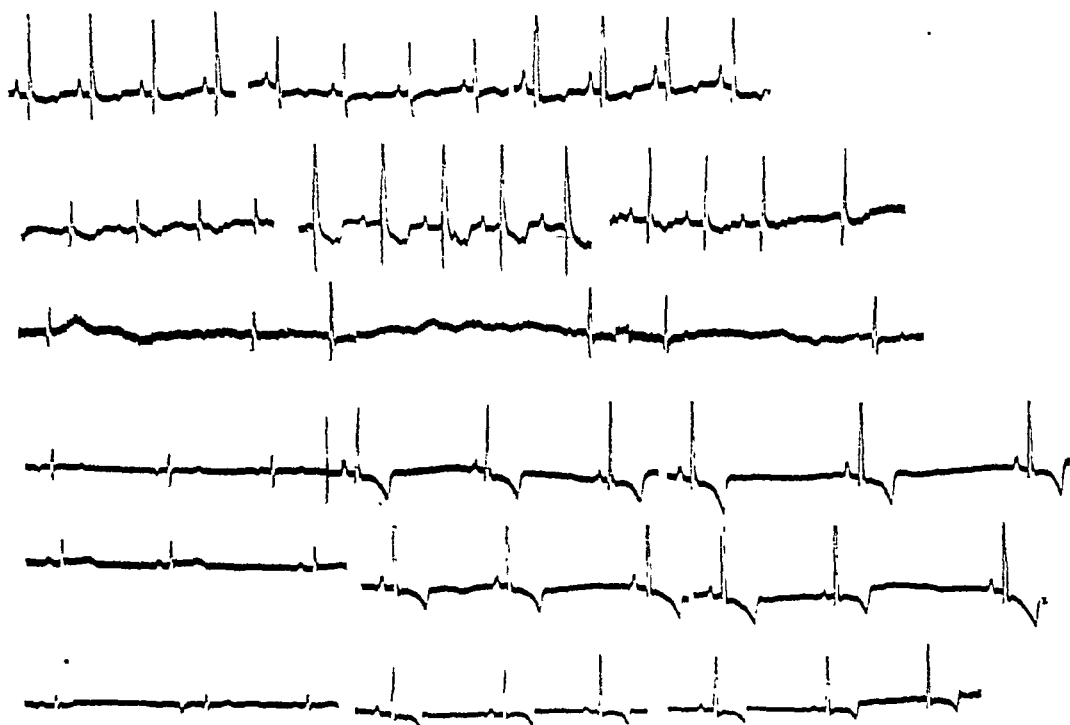


Fig. 9.—A typical experiment comparing the prolonged cardiac effects of unatropinized animals with those atropinized. Animals were treated with atropine before traction was exerted on the liver.

heart action after operation. It was then decided to make electrocardiograms on a number of animals to determine what changes could be observed in postoperative periods from the conditions noted in the same animals before operation. It may be seen in figure 7 that changes in the position of the animal do not cause significant changes in the contours of the electrocardiograms.

While this work was in progress, the work of Blumgart, Gilligan and Schlesinger⁹ appeared in which these investigators described ventricular fibrillation and extrasystoles resulting from temporary occlusion of a single coronary artery for varying periods. And they went further, to describe structural changes in the myocardium following (by a few days) the occlusions.

9. Blumgart, H. L.; Gilligan, D. R., and Schlesinger, M. J.: *Am. Heart J.* 22:374. 194

The problem, however, became one of explaining just how such changes in the normal function of the heart as are probable from the contours of the electrocardiograms shown in figure 8 could occur, since this work did not involve the heart or its blood vessels directly, as did that of Blumgart, Gilligan and Schlesinger. The theory seemed attractive that the changes were due to decreased venous return to the heart, which reduced the cardiac output and the coronary inflow. As a matter of fact, Wiggers¹⁰ in his recent review on the problem of shock pointed out that in shock there is depression of the myocardium which results from decreased cardiac output, although Katz (personal communication) objected to the view that coronary flow can be predicted from the cardiac output. Another, and more attrac-

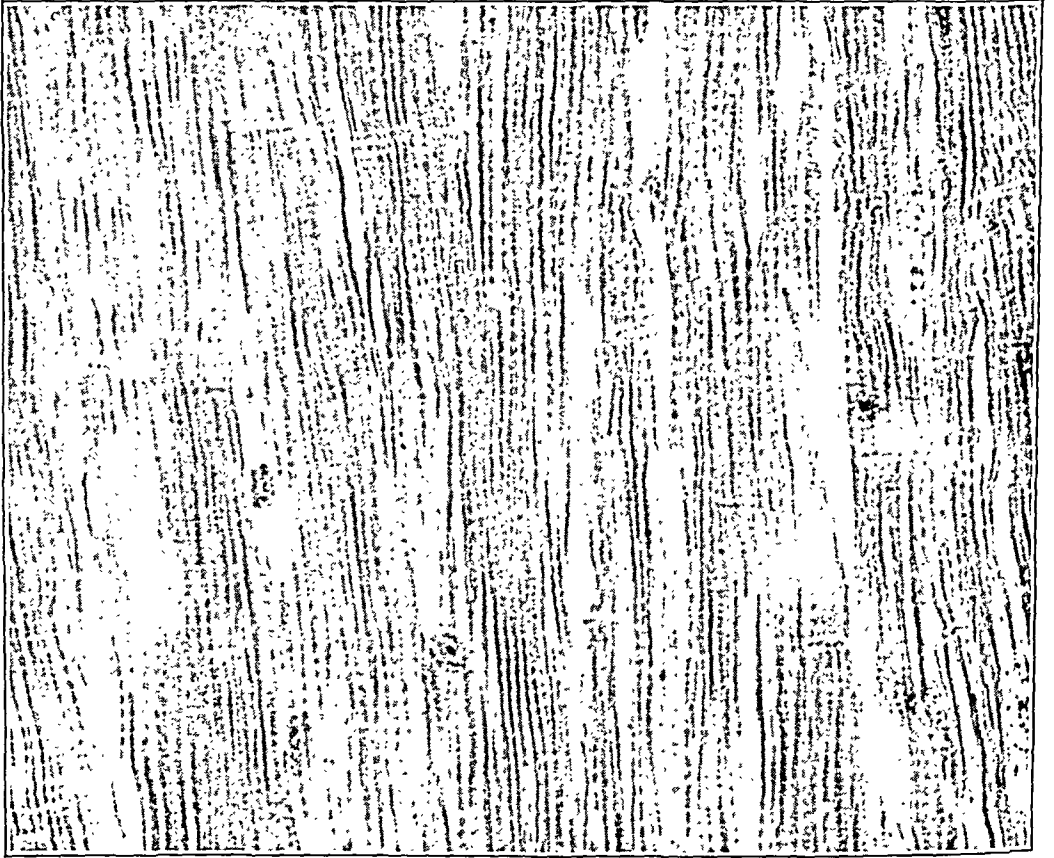


Fig. 10.—Photomicrograph of a histologic section of heart taken from an animal in which traction had been exerted on the liver. Note the nuclear degeneration. $\times 400$.

tive, point of view, however, was that the coronary arteries are supplied with vasoconstrictor fibers carried by the vagi (Lingle-Porter); and it seemed worth while to test the possibility that constriction of the coronary arteries might occur and act to reduce the blood supply to the heart. Thus blocking the action of the vagi with atropine should prevent constriction of the coronary arteries as well as the changes that occur in the electrocardiograms of the untreated animals (figs. 8 and 9). That the theory of vagal involvement during traction is tenable finds support in the work of Gilbert,¹¹ who described interesting experimental and clinical observations on

10. Wiggers, C. J.: *Physiol. Rev.* **22**:74, 1942.

11. Gilbert, N. C.: *Bull. New York Acad. Med.* **18**:83, 1942.

cardiac changes in dogs and in patients who had experienced different types of abdominal distention. He reported that patients who had hiatus hernias, and whose stomachs were definitely displaced and distended were known to experience anginal attacks and that patients with angina themselves were extremely susceptible to attacks immediately after a heavy meal. Atropinized animals failed to show extra-systoles or fibrillations when the stomach was distended with air, while the untreated animals showed such abnormalities.

The point advanced by Gilbert is that a vagal reflex is set up when the abdominal viscera are severely distended which acts to cause constriction of the coronary arteries and a corresponding reduction in the blood supply to the myocardium (causing a partial anemic infarct). This indeed seems to be a fitting explanation for the results described in this paper, although the histologic examination of the hearts taken from some of the animals failed to reveal more than nuclear degeneration (fig. 10).

SUMMARY AND CONCLUSIONS

Experiments are described which show the chronic effects resulting from downward traction on the liver.

The evidence seems to show that damage is done to the kidneys. The injury is probably produced by passive congestion (although possible reflex vasoconstriction is not to be excluded), and the result is renal hypertension which persists for months.

The changes in the contours of the electrocardiograms seem to point to the view that traction on the liver results in a derangement of the normal function of the heart, both during traction and weeks after. And there is mounting evidence that such manipulation sets up a reflex over the vagus nerve, which causes constriction of the coronary vessels, reducing blood supply and probably causing damage to the myocardium.

Apparently atropine blocks the reflex, for in atropinized animals no significant changes in the electrocardiograms occur either during traction or subsequently. (Such observations seem to indicate that atropine should be used in abdominal surgery not only for drying secretions but for eliminating the cardiac reflex).

Comparative histologic examination of sections from the myocardium of dogs which had been subjected to traction on the liver and similar sections from controls reveal apparent nuclear degeneration in the former.

Dr. Arno B. Luckhardt gave helpful suggestions for the carrying out of this study. Dr. G. W. Bartelmez prepared and interpreted the histologic material. Mr. Richard Johnson gave valuable technical assistance. Dr. Julian Lewis was responsible for some of the observations on the myocardium.

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REVIEW OF UROLOGIC SURGERY

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KIDNEY

Tumor.—Foulds¹ reports a case of renal tumor containing elements of malignant papillary cystadenoma and papillary carcinoma with clear cells. This case with other recorded cases illustrates the transition from renal adenoma to malignant cystadenoma and eventually, in some instances, to papillary carcinoma with clear cells.

The patient, a man 59 years of age, complained of pain and hematuria. The kidney was removed, and the patient recovered without difficulty. The kidney measured 13 by 7 by 4.5 cm. and weighed 225 Gm. The outer surface was slightly roughened and reddened. The capsule was thin and stripped with difficulty; the stripping left a finely granular surface. In the upper pole of the kidney, projecting into a calix, there was a soft red mass, measuring 4.5 cm. in length and 2.5 cm. in its greatest width. Microscopically the tumor was composed of papillary processes covered with small cuboidal cells, with deeply stained round or polyhedral nuclei. These processes projected into and nearly filled irregular cystic spaces. The stroma was densely fibrous. In one preparation made from the material removed for quick section, from the center of the tumor, small areas were found in which the cells were large and their cytoplasm clear or foamy. Small blood vessels were fairly numerous, and several small areas of calcification were seen. These areas in both the character and the arrangement of the cells presented a picture typical of papillary carcinoma with clear cells, the so-called hypernephroma. Preparations made from the edge of the tumor showed slight invasion of the adjacent renal tissue. There was hyperplasia of fibrous tissue between the tubules. Although the epithelium of the pelvis was reflected onto the edge of the tumor, it did not cover the projecting tumor. Sections taken from the remainder of the kidney showed little

1. Foulds, G. S.: An Unusual Kidney Tumor: Malignant Papillary Cystadenoma and Papillary Carcinoma with Clear Cells, *J. Urol.* 48:131-135, (Aug.) 1942.

of note except that the intima of the arterioles was thickened. The pathologic diagnosis was malignant papillary cystadenoma and papillary carcinoma with clear cells.

Beilin and Neiman² state that bilateral renal carcinoma in the adult is rare. They report the case of a man aged 50 years. The diagnosis of hypernephroma on the left side was made and the kidney removed in July 1933. Microscopic examination revealed hypernephroma. Six years later a diagnosis of renal tumor on the right side was made. Necropsy showed that the growth in the right kidney also was a hypernephroma.

Vitt and Melick³ review 6 cases of hypernephroma of the kidney as a complication of pregnancy which have been reported in the literature and add a case of their own. The diagnosis of renal tumor should be made, if possible, before the classic triad of pain, mass in the loin and hematuria have appeared. However, even if these are present operation in carefully selected cases can prolong life. Whether the growth of renal tumors is accelerated by coexisting pregnancy and the lesion is more likely to metastasize during pregnancy cannot be settled definitely. Pregnancy usually is not terminated by removal of a kidney and is not a contraindication to operation, provided the other kidney is normal. Further pregnancies are possible, provided that the function of the remaining kidney is normal and every precaution is taken during the subsequent pregnancies to watch for, and to guard against, renal insufficiency and infection.

Colvin⁴ studied and tabulated the characteristics of 164 capsulomas (small, benign, mixed capsular and subcapsular tumors of the kidney) in 144 of 2,634 consecutive patients who came to necropsy at the Mayo Clinic—an average incidence of 5.5 per cent in the period of four years covered by the study. The incidence apparently varies in proportion to current interest. Ninety-nine per cent of the 164 patients were more than 40 years of age. There was no appreciable variation in sex incidence. From one to three capsulomas were found per patient, but the majority were single. Capsulomas occurred with approximately equal frequency in the right and the left kidney. They were located in or just under the renal capsule. Their diameters varied from 1 to 5 mm. Histologically, they contained two basic elements, smooth muscle and fibrous tissue, although a certain proportion contained fat and epithelial elements. All tumors in this series were benign; they were apparently of no clinical significance and were discovered incidentally at necropsy. According to the evidence gathered, it is believed that capsulomas are true tumors; some are derived from the capsule, some from nephrogenic rests and a few from the walls of blood vessels.

Stone.—Dourmashkin and Solomon⁵ state that lithiasis of the upper part of the urinary tract is a common complication of urethral stricture. It occurred in 22.6 per cent of cases in their series. In 6 of the 9 cases of renal stone and in 2 cases in which advanced renal lesions other than stone were present, renal pain was absent; the lesions were discovered through routine roentgen examination. Because patients who have stricture are of the transient type, Dourmashkin and Solomon

2. Beilin, L. M., and Neiman, B. H.: Bilateral Renal Carcinoma, *J. Urol.* **48**:575-584 (Dec.) 1942.

3. Vitt, A. E., and Melick, W. F.: Carcinoma of the Kidney and Pregnancy, *J. Urol.* **48**:601-610 (Dec.) 1942.

4. Colvin, S. H.: Certain Capsular and Subcapsular Mixed Tumors of the Kidney Herein Called "Capsuloma," *J. Urol.* **48**:585-600 (Dec.) 1942.

5. Dourmashkin, R. L., and Solomon, A. A.: Upper Urinary Tract Lithiasis: A Frequent Complication of Urethral Stricture, *J. Urol.* **48**:196-203 (Aug.) 1942.

suggest that an immediate roentgen examination of the urinary tract should be done when the diagnosis of a stricture is established.

Hypertension and Renal Lesions.—Ratliff and Conger⁶ present statistics based on a series of 528 consecutive hypertensive persons. Unsuspected lesions of the kidney were demonstrated in a low but sufficiently high percentage of cases to warrant continuance of routine pyelographic studies in cases of asymptomatic hypertension as well as in cases in which urinary symptoms are present.

Ratliff and Conger evaluate the results of nephrectomy in selected cases of hypertension. They consider that the point of major importance is the selection of the case. For the time being, and until a more selective test has been adopted, a policy should be adopted that nephrectomy should be performed in any case of hypertension in which unilateral renal disease can be demonstrated, not only in order to cure the local lesion but in the hope that the hypertension will be relieved.

Braasch and Wood⁷ report a survey of the records of 70 cases of clinical perinephritis in an effort to determine the effect of this condition on blood pressure. Fifty-two of the 70 patients were males, and 18 were females—a ratio of 2.89 to 1. The mean age for the group was 38.3 years. Eighty-one and four-tenths per cent of the group were less than 50 years of age. In 67 of the cases the diagnosis was verified through surgical exploration; in the 3 remaining cases the clinical and urographic evidence was sufficient to warrant the diagnosis, although the treatment was conservative.

Six patients were classed as hypertensive by virtue of elevation of the systolic or diastolic blood pressure or both. This is an incidence of 8.6 per cent. In 2 of these 6 cases, however, conclusive evidence was present that hypertension had existed prior to onset of the perirenal disease. One of these patients had known for twenty years that he had hypertension; the other, for at least two years. In a third case other factors apparently were operating to influence the arterial blood pressure and, although the blood pressure was 114 mm. of mercury systolic and 90 mm. diastolic at the time of drainage of the perirenal abscess, one year later it had increased to 148 mm. systolic and 90 diastolic. Thus only 3 cases remain in which association of perinephritis and elevated arterial blood pressure might be present, an incidence of but 4.3 per cent.

A second group of cases of perinephritis secondary to some primary renal disease, such as renal lithiasis or hydronephrosis or both, or pyonephrosis, was reviewed for evidence of association of elevated blood pressure. The cases in this group were selected according to the degree of perinephritis present, the blood pressure being ignored until the group analysis was begun. In 28 cases the perinephritic reaction was considered to be of sufficient degree to warrant inclusion in this group. In 6 (21.4 per cent) of these 28 cases, hypertension was present.

Aneurysm.—Child⁸ presents a case of aneurysm of the renal artery, which brings the total number of reported cases to 75. The chief interest in this lesion, aside from its rarity, lies in the confusion of the wreathlike shadow of calcium density seen in this case with that cast by a gallstone, which led to an erroneous preoperative diagnosis and an unnecessary celiotomy. A careful study of this patient's preoperative and postoperative blood pressure failed to reveal any relationship between them and the aneurysm.

6. Ratliff, R. K., and Conger, K. B.: The Incidence of Renal Hypertension and of Cure by Nephrectomy, *J. Urol.* **48**:136-141 (Aug.) 1942.

7. Braasch, W. F., and Wood, W. W., Jr.: Clinical Perinephritis and Its Effect on Blood Pressure, *J. Urol.* **48**:343-349 (Oct.) 1942.

8. Child, C. G., III: Aneurysm of the Renal Artery: A Case Report, *J. Urol.* **48**:142-146 (Aug.) 1942.

Ischemia.—Hoffman⁹ reports a case of renal ischemia produced by aneurysm of the abdominal aorta. The patient was a Negro aged 28 years who had late syphilis. He was dyspneic and died from congestive heart failure. At necropsy an aneurysm about 6 cm. in diameter was found extending out from the left side of the abdominal aorta. This aneurysm pressed on and stretched the vessels of the left kidney and considerably diminished the lumen of the renal artery. About half of the aneurysm was filled with blood clot. The left kidney weighed only 80 Gm.

This case is interesting in that the conditions which Goldblatt produced in his experimental work on dogs also were produced in this case. The blood pressure was 190 mm. systolic and 117 diastolic, quite possibly owing to the ischemia of the left kidney and renal damage caused by the diminution in size of the lumen of the left renal artery.

Life After Nephrectomy.—From a review of the data obtained in his study of cases of nephrectomy, Kretschmer¹⁰ makes the following statements:

The average length of time that elapsed between nephrectomy and examination was eight years and two months. The longest period since the nephrectomy in his series was twenty-four years and eleven months.

The oldest patient at the time of nephrectomy was 72 years of age; one year and eight months had elapsed since the operation. The oldest patient studied in this series was 77 years of age; a period of sixteen years had elapsed since the operation. The youngest patient at the time of nephrectomy was 10 months of age; a period of four years and six months had elapsed since the operation.

Pain in the remaining kidney does not occur with any great regularity, although the impression seems to prevail that this phenomenon is common after nephrectomy. It occurred in only 7 cases in this series. In some of the cases in which it occurred, a pathologic condition in the remaining kidney, disclosed by study, was responsible for its presence.

Eighteen patients (11.5 per cent) had cardiac involvement, 4 of whom were less than 50 years of age. One patient had cardiac hypertrophy before operation. The incidence of cardiac enlargement in a group of patients more than 50 years of age after nephrectomy is therefore about what one can expect in a group of persons of similar ages who had not undergone nephrectomy.

In the largest number of cases weight remained the same or there was an increase. In only 5 was there a loss. A gain of as much as 50 pounds was noted in 7 cases.

In 14 cases there was an increase in the blood pressure. After elimination of the cases in which hypertension was present before operation, the study discloses that the patients were well along in years, having reached a time in life when hypertension might be expected.

The results of urinalysis depend on the lesion for which the nephrectomy was performed. Of the 49 cases of renal tuberculosis, pus was present in 14 and albumin in 6. Of the 42 cases of stone, pus was present in 11 and albumin in 6, whereas in the remaining groups of 65 cases pus was present in 11 and albumin in 6. The cultures were more frequently positive in the group of cases in which nephrectomy had been performed for stone. All cultures of urine in the cases of tumor were sterile. Cultures of urine were positive in 4 cases in the miscellaneous group, in 11 cases of hydronephrosis and in 14 cases of tuberculosis.

9. Hoffman, B. J.: Renal Ischemia Produced by Aneurysm of Abdominal Aorta, J. A. M. A. **120**:1028-1030 (Nov. 28) 1942.

10. Kretschmer, H. L.: Life After Nephrectomy, J. A. M. A. **121**:473-478 (Feb. 13) 1943.

Studies of the nonprotein nitrogen content of the blood were made in 146 of the 156 cases. The value was increased in 36 (24.65 per cent).

Seventy-three per cent of the patients with only one kidney were able to pass the Newburgh concentration test.

Circulation and Pitressin.—Wakim, Herrick, Baldes and Mann¹¹ studied the effect of pitressin on renal circulation and urinary secretion of frogs and dogs. Various dilutions of pitressin were administered to anesthetized frogs by three methods—direct application to the kidney, injection into the dorsal lymph sac and injection into the abdominal vein. By means of transillumination, direct observations were made on the glomerular tuft of capillaries and other vessels. These authors found that pitressin produced cessation of circulation in the glomerular tuft and slowed the circulation in the other vessels for a fraction of a minute to several minutes, depending on the amount and dilution of pitressin used.

Two groups of dogs under different types of anesthesia were given pitressin by various methods. Simultaneous records of urine formation and renal blood flow and optical records of blood pressure were made. No changes were noted when pitressin was administered subcutaneously. Intramuscular administration produced only slight changes. When pitressin was injected intravenously, transient anuria resulted and was followed by oliguria and marked decrease in renal blood flow and a sudden transient rise in blood pressure which was eventually followed by a gradual but moderate rise. The authors conclude that the intravenous administration of pitressin invariably decreases the blood flow and urge caution when using the drug in this manner to prevent untoward effects.

URETER

Tumor.—Moore¹² states that both benign and malignant neoplasms occur in the ureter, but the latter are much more common and may be of either epithelial or connective tissue origin. For simple papilloma, if adequate care is taken not to infect other tissues at operation, the prognosis is good. The outlook for carcinoma is bad. The growth is usually advanced before the diagnosis is made, and there is a considerable immediate operative mortality. The only rational treatment is complete ureteronephrectomy. This usually can be performed safely in one stage with the patient under spinal anesthesia. When the complete operation is performed, there are two ways of dealing with the lower end of the ureter. It may be excised with a small portion of vesical wall, or the extreme lower end may be left, its mucosa being destroyed by diathermy before ligation in order to destroy any neoplastic deposits in it.

Moore reports the case of a man aged 25 years who had pain in the left renal area for fifteen months. Intravenous urography revealed some dilatation of the lower part of the left ureter, which had a peculiar mottled appearance. Complete nephroureterectomy was done except for the lowest $\frac{1}{4}$ inch (0.64 cm.) of the ureter. The mucosa of the lower end of the ureter was destroyed with diathermy before ligation. Microscopic examination showed a simple papilloma of the ureter.

Moore also reports a case in which retrograde ureterograms showed an irregular obstruction in the middle of the left ureter of a man aged 57 years. At operation a hard nodule was found in the middle portion of the left ureter. The ureter was

11. Wakim, K. G.; Herrick, J. F.; Baldes, E. J., and Mann, F. C.: The Effect of Pitressin on Renal Circulation and Urine Secretion, *J. Lab. & Clin. Med.* **27**:1013-1022 (May) 1942.

12. Moore, T.: Tumors of the Ureter, *Brit. J. Surg.* **29**:371-377 (April) 1942.

ligated below this and mobilized as high up as possible. The wound was closed and the operation completed through the ordinary oblique kidney incision. The growth in this case was malignant.

Sauer¹³ reports a case of metastasis to bone from carcinoma of the ureter complicated by congenital hydronephrosis. The patient was a man 56 years of age who gave a history of pain in the right loin and a tumor mass in the right side of the abdomen. After cystoscopic examination, a diagnosis was made of tumor of the right kidney with metastasis to the right humerus. The patient died and two different conditions were found: one was a combination of congenital anomalies; the other was carcinoma of the ureter which had metastasized to the right humerus and to the left kidney. There was complete duplication of the renal pelvis and ureter on the left side, with the calices of the lower renal pelvis pointing toward the midline. On the right side massive hydronephrosis was found, which obviously was due to congenital stricture at the ureteropelvic junction. The hydronephrotic sac contained 1,500 cc. of bloody, foul-smelling urine. The lumen of the middle third of the right ureter was filled by a papillary tumor which was 4.5 cm. long and from 2.3 to 2.8 cm. wide. A distance of 1.5 cm. separated the upper border of the tumor from the stricture at the ureteropelvic junction. No infiltration of the ureteral wall by the tumor was apparent between the stricture and the upper border of the neoplasm. Examination of the right humerus revealed almost complete replacement of its upper third by tumor tissue. The lesion, which was 12.5 cm. long and 8.5 cm. wide, had the macroscopic appearance of an osteogenic sarcoma. No other metastatic lesions were found except a small one in the left kidney. Microscopic examination of the primary tumor revealed papillary carcinoma of the squamous cell type, which had invaded the deeper layers of the ureteral wall. Sections from the lesions of the right humerus and the left kidney showed the same histologic structure as the primary growth.

Riches¹⁴ reports a case of carcinoma of the ureter in a woman 46 years of age. Excretive urography revealed a small calculus in the lower end of the right ureter with some dilatation of the kidney and extensive hydronephrosis of the left renal pelvis. The stone was passed after cystoscopic manipulation, and further catheterization revealed an obstruction 15 cm. above the orifice. A diagnosis of ureteral tumor was made and nephro-ureterectomy carried out. In the ureter there was a firm fusiform mass to which the overlying peritoneum was adherent. The specimen removed showed a hydronephrotic kidney, with dilatation of the upper portion of the ureter and a papillary growth which constricted the ureter directly below this. Recurrence developed, and the patient died several months later.

Transplantation.—Jewett¹⁵ discusses a new method of ureteral transplantation. At the first operation, the intestinal bed is prepared for the ureter. The incision, 5 cm. in length, is carried down to the submucosa. The lateral edge of the incision is peeled up for a distance of 0.5 cm., and the medial edge, for 2 mm. The ureter is completely extraperitonealized. Both ureters are buried in the wall of the bowel and left connected with the bladder at the first operation. No communication is made between the ureter and the intestinal lumen at this time. Three weeks later the second operation is carried out. The ureter is cut off from its

13. Sauer, H. R.: Case of Large Bone Metastasis from Carcinoma of the Ureter Complicated by Congenital Giant Hydronephrosis, *J. Urol.* **48**:467-473 (Nov.) 1942.

14. Riches, E. W.: A Case of Primary Carcinoma of the Ureter, *Brit. J. Surg.* **29**:392-393 (April) 1942.

15. Jewett, H. J.: A New Method of Ureteral Transplantation for Cancer of the Bladder: A Report of Fifteen Clinical Cases, *J. Urol.* **48**:489-509 (Nov.) 1942.

connection with the bladder; the lower end is ligated, and an electrode is placed in the lower end of the ureter to burn through into the intestinal lumen.

Jewett carried out this procedure with a specially insulated electrode in a series of 15 cases. Nine of the patients are now living, and the longest post-operative interval is eighteen months. Of the 6 patients who died, 3 died during convalescence and 3 later. Four had complications which required further operations. Laparotomy in 1 case disclosed volvulus of the intestine. In the second case the ureteral stump was torn out of its intestinal tunnel at the second stage, and eventually cutaneous ureterostomy had to be done. Excessive traction was the cause, and this has been avoided in succeeding cases. In the third case a chronic pelvic abscess occurred and was drained three and a half months after cystectomy. The subsequent course was entirely uneventful. The fourth case was that of a middle-aged woman who had had eight previous abdominal operations. On the left side there were chronic pyelitis and ureteritis prior to transplantation, and the urine contained *Streptococcus faecalis*. After the second stage of the transplantation of the left ureter, some intra-abdominal extravasation of urine occurred, which required drainage and subsequent nephrectomy. Further progress of the patient has been satisfactory.

BLADDER

Tumor.—Spencer¹⁶ reports a case of mucoid adenocarcinoma of the urinary bladder and gives a résumé of the literature. The patient was a young man aged 23 years. Cystoscopy revealed an encrusted tumor of the right anterior wall of the bladder. At operation a growth the size of a walnut was found in the apex of the bladder. The tumor was excised and the wall of the bladder sutured. Histologic examination revealed mucoid adenocarcinoma. Two and a half years later the tumor recurred and a hard, fixed suprapubic mass was found. A second operation was carried out.

Graham¹⁷ discusses ectopia vesicae complicated by adenocarcinoma and reviews the literature. Ectopia vesicae is an uncommon congenital deformity. Fifty per cent of all persons afflicted with exstrophy are dead by their tenth year, and 66.67 per cent are dead by their twentieth year. In one series reported in the literature, out of 74 patients not operated on, only 23 passed the twentieth year of life. It is estimated that about 10 per cent reach maturity, and in a few of this number carcinoma of the exposed bladder develops.

Tumors of the adenomatous type are rare in the normal bladder. Tumors most closely resembling those found in the ectopic bladder are found at the apex of the bladder. The structure of the wall of the ectopic bladder presents a different appearance from that of the normal bladder. Superficially there are thickening and keratinization of the epithelium which cause it to resemble epidermis, while in the deeper layers is glandular tissue formed by high cylindric epithelium, with mucus-containing goblet cells. This glandular formation, which has been noted in all the cases in which microscopic examination has been performed, would appear to be usual to the ectopic bladder, whereas it is exceptional in the normal bladder. Thus the high incidence of adenocarcinoma of the intestinal type in the ectopic bladder is accounted for.

In order to verify the statements and to offer some explanation as to the origin of the adenomatous tissue, a small series of ectopic bladders from patients of varying ages was collected and histologic examination was carried out by Graham.

16. Spencer, H.: Mucoid Adenocarcinoma of the Urinary Bladder, *Brit. J. Surg.* **29**: 400-402 (April) 1942.

17. Graham, W. H.: Ectopia Vesicae Complicated by Adenocarcinoma, with a Review of the Literature, *Brit. J. Surg.* **30**:23-32 (July) 1942.

The bladder of the youngest patient, aged 4 months, revealed a transitional cell lining which was hyperplastic and keratinized in places. Transitional cell epithelial nests were seen deep in the hyperplastic lining, and one had undergone cystic change. In the same sections a larger cyst could be seen, the lining, of which, although of transitional cells, was somewhat modified. The specimen of bladder from a child 6 years old had a lining which in places was keratinized and squamous in character. There were numerous cystic spaces, some lined by transitional epithelium and others by a single layer of flattened epithelial cells. One area contained glandular tissue lined by tall columnar celled mucin-secreting epithelium. Two specimens from patients aged 45 and 48 years respectively showed a similar lining, but the submucous layers contained a much larger proportion of glandular tissue.

Graham¹⁷ also reports 2 cases of exstrophy of the bladder complicated by adenocarcinoma. He states that the adenomatous tissue in the ectopic bladder is of a precancerous nature and the bladder must be removed. The growth remains locally malignant until well advanced, and metastatic growths are rare. The operation of choice is excision of the bladder preceded or followed by transplantation of the ureters into the rectum.

Kreutzmann¹⁸ reports a case of primary lymphosarcoma of the bladder and states that it is a rare condition, only 4 cases having been reported. He expresses the belief that lymphosarcoma originates from the lymphoid tissue in a chronically irritated bladder. Lymphosarcoma of the bladder is a localized condition without evidence of generalized glandular enlargement. Early diagnosis and radical excision will give the most favorable results.

Wheelock¹⁹ reports 5 cases of sarcoma of the urinary bladder. The diagnoses in all cases were proved by histologic examination. All patients died and 4 postmortem examinations were performed. Two of the 5 patients were women and 3 were men. All were more than 50 years of age. The sarcoma in all 5 cases originated in the lower half of the bladder. Similarly, there was more extensive involvement of the posterior than of the anterior portion of the bladder.

In the gross, the tumors were everted growths at the same time that they infiltrated the walls. Two invaded extravescical tissues. In the 3 cases in which resection was tried there was rapid recurrence. Response to irradiation was unsatisfactory.

In these cases the courses were unusually rapid; the longest was eighteen and the shortest five months. All the patients consulted physicians because of bleeding with other associated symptoms of disease of the lower part of the urinary tract. In the 4 cases in which necropsy was performed, some form of cystitis or pyelonephritis was present and death was attributed to renal insufficiency. No metastasis was found. There was invasion of the perivesical tissues in 1 and of the prostate gland in another.

In brief, additional information derived from a study of the data of investigators is as follows: Nonepithelial tumors of the bladder are infrequently encountered, and of these sarcoma is most rare. The lesion is seen most frequently in the young and next in the old. Sarcomatous tumors of the bladder select the trigone and base. Grossly, they are single or multiple, sessile or pedunculated, soft and friable, usually large, often ulcerated, rapidly growing and invasive. They metas-

18. Kreutzmann, H. A. R.: Primary Lymphosarcoma of the Bladder. *J. Urol.* **48**:147-152 (Aug.) 1942.

19. Wheelock, M. C.: Sarcoma of the Urinary Bladder. *J. Urol.* **48**:628-634 (Dec.) 1942.

tasize in 23 per cent of the cases, usually to the liver, the inguinal and regional lymph nodes and the lungs. They are nearly always fatal. Although intimate relation of tumor cells to blood vessels has been noted often, actual invasion and vascular dissemination are uncommon. Death results from obstruction, ascending infection to the kidneys and renal insufficiency.

Buschke and Cantril²⁰ report 52 cases in which advanced carcinoma of the bladder was treated between 1934 and 1940 with 800 kilovolt roentgen irradiation. All controlled cases in this series were cases of papillary carcinomas without infiltration of the musculature of the bladder. Extensive papillary growths in which infiltration cannot be demonstrated are the most suitable for roentgen therapy. The majority of the patients had been received after one or more unsuccessful fulgurations for papillary carcinomas. The single papilloma of the bladder can be destroyed by fulguration. It is, however, the experience of every urologist that these isolated papillomas tend to recur in other areas of the bladder and from the clinical point of view they are papillary carcinomas rather than papillomas. In certain of Buschke and Cantril's cases in which the papillary growths had recurred after repeated fulgurations roentgen therapy had arrested this process. They therefore feel that those papillary carcinomas of the bladder which either tend to recur or have recurred after one fulguration should be treated with roentgen rays without further delay if this type of treatment is considered at all.

In none of Buschke and Cantril's cases of infiltration of the tumor into the muscle was sterilization performed, regardless of whether the lesions were originally papillary growths with secondary invasion or primarily infiltrating tumors.

External roentgen therapy of the type described for carcinoma of the bladder is a formidable undertaking. It can be conducted with any hope of success only in cases in which the general condition of the patient will support such a major procedure. Good general condition, adequate drainage from the bladder, adequate capacity and absence of extensive infection are prerequisites for a fair trial of this method. A previous suprapubic operation, particularly in the presence of any obstruction or infection, is an additional hazard to intense irradiation. This is not a procedure suitable for palliative purposes only. Patients who have lesions inoperable because of extravesical extension have not been benefited.

Atkinson²¹ discusses metastasis to the skin from tumors of the bladder. This type of metastasis is comparatively rare, only a few cases having been reported. Atkinson records the case of a 59 year old man who had a tumor about 2.5 cm. in diameter in the bladder. Grossly the tumor was a papilloma; histologically it was diagnosed as papillary carcinoma. Six weeks later a small nodule appeared on the patient's upper lip. Biopsy showed this to be similar to the growth in the bladder.

Glandular Proliferation.—Emmett and McDonald²² report 9 cases of proliferation of glands of the urinary bladder simulating malignant neoplasm. All of the 9 patients except 1 complained of varying degrees of dysuria; all except 1 had suffered from hematuria. Urinary infection was present in all but 1 case, while

20. Buschke, F., and Cantril, S. T.: Roentgentherapy of Carcinoma of Urinary Bladder: An Analysis of Fifty-Two Patients Treated with Eight Hundred K. V. Roentgentherapy, *J. Urol.* **48**:368-383 (Oct.) 1942.

21. Atkinson, R. C.: Skin Metastases from Bladder Tumors, *J. Urol.* **48**:350-356 (Oct.) 1942.

22. Emmett, J. L., and McDonald, J. R.: Proliferation of Glands of the Urinary Bladder Simulating Malignant Neoplasm, *J. Urol.* **48**:257-265 (Sept.) 1942.

leukoplakia and vesical calculus each were present in 1 case. In all but 2 cases the cystoscopic appearance of the bladder suggested the presence of a malignant tumor.

Histologically, two distinct types of glands were present. In one type, termed "intestinal type of glands," the acini were lined by a simple layer of columnar epithelium indistinguishable from the goblet cells of the intestinal tract. In the other type, termed "glands of subtrigonal type," the acini were lined by multiple layers of cells, consisting of a single layer of columnar cells adjacent to the lumen of the gland which was surrounded by several layers of stratified squamous epithelium. The latter type is often referred to as the "glands of Albarran." Mucus was demonstrated in both types of glands. Various stages of cystic formation were found in the subtrigonal type. Evidence of inflammatory cells was found in nearly every instance. Emmett and McDonald could not see any similarity between subtrigonal and prostatic glands. In nearly all of their cases the lesions involved the trigone or base of the bladder. They believe that these glands are formed by metaplasia from the epithelial lining of the urinary bladder and may proliferate when associated with inflammation.

Most of their patients responded to treatment consisting of vesical lavage, urinary antiseptics and fulguration.

Embryology of the Muscle of the Vesical Neck.—Trabucco,²³ in discussing the embryology of the muscle of the vesical neck, states that the lower lip of the vesical neck is of mesenchymatous origin. Its development bears no relation to that of the embryonic entodermic sheet. In the rabbit embryo of 18 days, the mesoblastic cellular tissue begins to differentiate into smooth muscle. In the rabbit fetus of 27 days there is a true small muscle with all the adult characteristics. In the smallest human embryo, 8 mm. long, some orientation of the mesenchymatous cells is already noticeable. In the 12 mm. human embryo the mesenchymatous cells tend to be transversally placed before the opening of the wolffian ducts. In the 20 mm. human embryo, the thickening of the area studied is more marked. In the 30 mm. human embryo transverse orientation of the cells in a small cellular band is observed. In the 35 mm. human embryo this band is 60 microns thick. Transformation of the cells that will constitute the muscle of the vesical neck into smooth muscle fibers begins in the 52 mm. human embryo. In the 8 cm. human fetus a true small muscle is apparent. In the human fetus of 4 months the muscle of the lower lip of the vesical neck is clearly differentiated. In a full term human fetus the muscle proper of the vesical neck is perfectly well differentiated, having all the adult characteristics.

PROSTATE GLAND

Carcinoma.—Alyea and Henderson²⁴ during the past year treated 40 patients with carcinoma of the prostate by castration. A follow-up study in all but 1 case showed a low mortality rate. The immediate clinical results in all cases were most encouraging. One patient had a relapse and extension of the tumor after eight months of comfort.

The subjective signs of improvement after castration are increase in appetite, well-being and energy, relief of metastatic pain, relief of urinary obstruction, disappearance of infection and stopping of recurrent hemorrhage.

Objective clinical and laboratory signs of improvement and regression of the tumor after castration are lowering of the serum "acid" phosphatase, roentgeno-

23. Trabucco, A.: Embryology of the Vesical Neck Muscle, *J. Urol.* **48**:153-162 (Aug.) 1942.

24. Alyea, E. P., and Henderson, A. F.: Carcinoma of the Prostate: Immediate Response to Bilateral Orchiectomy; Clinical and X-Ray Evidence, *J. A. M. A.* **120**:1099-1102 (Dec 5) 1942.

graphic signs of bone healing at the site of the metastatic lesion and disappearance of pulmonary metastatic lesions.

Diethylstilbestrol causes a response similar to castration but not of the same degree. Alyea and Henderson favor castration first and reserve treatment with diethylstilbestrol for patients who show evidence of extragonadal hormone activity or refuse castration.

Creedy²⁵ states that the number of cases of carcinoma of the prostate gland is increasing, not because of increased individual susceptibility but because of increasing longevity. Its prognosis is poor. The early lesion can be recognized if every small hard nodule in the prostate is subjected to careful study, including biopsy. Aspiration biopsy is least useful when most needed; that is, for small nodules of doubtful character. Treatment may be symptomatic, but radical perineal prostatectomy alone offers any real hope of cure, although its rate of applicability is low. Creedy is of the opinion that widespread trial of radical perineal prostatectomy should be made in properly selected early cases.

Nesbit and Cummings²⁶ report a series of 75 cases of prostatic carcinoma treated by orchiectomy in which the patients were observed for at least six months. Elevation in the serum "acid" phosphatase was observed in 39 per cent of the cases. Favorable response, as determined by both subjective and objective criteria, was observed in 73 per cent of cases.

There were 20 failures. Four patients died of carcinoma and 1 from congestive heart failure and infection. For 15 living patients the treatment is considered to have failed; 5 showed no favorable response at any time following operation, while the results for 10 are considered delayed failures because they enjoyed freedom from all subjective evidences of their disease for periods of three to twenty-two months after gonadectomy before symptoms recurred.

Nesbit and Cummings observed no satisfactory criteria for prognosticating the results of orchiectomy for carcinoma of the prostate. The occurrence of 10 delayed failures in this series of cases, with postoperative relapse at periods of from three to twenty-two months, offers disquieting implications regarding the ultimate outcome in any case. Regardless of these implications or of the possibility of failure in some cases, it is evident that gonadectomy is a worth while procedure for advanced prostatic cancer and should be recommended when the diagnosis is established.

Gutman,²⁷ in discussing the finding of serum "acid" phosphatase in cases of carcinoma of the prostate gland, states that it occurs in and is apparently elaborated by the acinar epithelium of the prostate gland. The concentration of the enzyme in prostatic tissue of adult human beings is extraordinarily high (500 to 2,500 units of activity per gram of fresh tissue), many hundred times that of any phosphatase in kidney, liver, duodenal mucosa or bone. The enzyme does not appear in appreciable amount in prostatic tissue of human beings or monkeys until puberty. Prostatic "acid" phosphatase normally is excreted as a constituent of the prostatic fluid; high concentrations are present in seminal plasma of human beings.

Apart from occasional highly undifferentiated prostatic tumors which do not elaborate the enzyme, carcinomatous prostatic tissue contains large amounts of "acid" phosphatase. This holds not only for tumor tissue at the primary site

25. Creedy, C. D.: The Diagnosis and Treatment of Early Carcinoma of the Prostate, *J. A. M. A.* **120**:1102-1105 (Dec. 5) 1942.

26. Nesbit, R. M., and Cummings, R. H.: Prostatic Carcinoma Treated by Orchiectomy: A Preliminary Report Based on Seventy-Five Cases Observed for at Least Six Months Following Operation, *J. A. M. A.* **120**:1109-1111 (Dec. 5) 1942.

27. Gutman, A. B.: Serum "Acid" Phosphatase in Patients with Carcinoma of the Prostate Gland: Present Status, *J. A. M. A.* **120**:1112-1116 (Dec. 5) 1942.

but also for distant metastatic processes. The presence of so much "acid" phosphatase in metastatic lesions secondary to prostatic carcinoma may have some causal relation to the osteoplastic character of most such metastatic lesions in bone.

When carcinoma of the prostate gland metastasizes, invasion of lymph or blood channels is accompanied by escape of the prostatic secretion into the circulation. Because of its high "acid" phosphatase content, prostatic secretion present in blood can readily be detected by means of appropriate chemical methods for estimating the "acid" phosphatase activity of blood serum, which is increased by influx of the prostatic enzyme. This forms the theoretic basis for the now widely used determination of serum "acid" phosphatase in the differential diagnosis of metastasizing prostatic carcinoma.

The effect of castration and estrogens in cases of metastatic prostatic carcinoma constitutes what is perhaps the most rigorous proof yet submitted that malignancy is not necessarily the result of an irreversible urge to grow intrinsic to the tumor cell but may be due in part to stimulation by extrinsic (in this instance endocrine) agents which are subject to some measure of therapeutic control.

Elevated values were obtained in about 85 per cent of a total of 177 cases of proved or suspected metastasis from prostatic carcinoma. About 90 per cent of patients with carcinoma of the prostate but without roentgenographic evidence of involvement of bone gave values consistently less than 3 units, as did all normal subjects, all patients with prostatic disease other than carcinoma and more than 90 per cent of a total of 853 patients with nonprostatic disease. Falsely high serum "acid" phosphatase values occurring in cases of diseases other than prostatic carcinoma with metastasis most commonly result from the use of hemolyzed serums.

There is no correlation between the levels of "acid" and "alkaline" phosphatase in the serum in cases of prostatic carcinoma except that the concentration of both is normal before dissemination of the tumor and usually above the normal maximum after metastatic spread has occurred. The increase in serum "alkaline" phosphatase is of osseous origin and reflects the extent and vigor of the osteoplastic reaction of bone at the site of the skeletal metastatic processes; if the liver also is involved, a further increase in serum "alkaline" phosphatase may result from obstruction to excretion of the enzyme in the bile.

The method is incapable of detecting prostatic carcinoma which has not yet metastasized and is therefore of no value in the important problem of differentiating that condition from benign prostatic hypertrophy.

Only meager data are available regarding the effect of estrogens on the serum phosphatases in cases of metastatic spread of carcinoma of the prostate. These make it clear, however, that estrogens in appropriate dosage generally cause a fall in serum "acid" phosphatase and a delayed rise in serum "alkaline" phosphatase.

Herbst²⁸ states that the biochemical control of carcinoma of the prostate gland is based on the principle of the maintenance of low levels of androgen and "acid" phosphatase in the blood. Testosterone elevates blood phosphatase and therefore should be administered with caution to men. The dose of estrogens to be administered should not be more than that required to maintain control of the malignant process, which is a variable and individual quantity. In some instances the malignant process may be accelerated rather than controlled by diethylstilbestrol. Should the prostatic carcinoma of patients who have been castrated cease to remain latent, as has occurred in carcinoma of the breast following bilateral oophorectomy, it would seem likely that additional control may be maintained by

²⁸ Herbst, W. P. Biochemical Therapeutics in Carcinoma of the Prostate *Gland. J. A. M. A.* 120:1116-1120 (Dec. 5) 1942

giving estradiol dipropionate or diethylstilbestrol and possibly other biochemical agents not yet utilized or available. These relatively simple methods of biochemical control of prostatic carcinoma should have a wide field of application even though the control cannot be maintained indefinitely. The relief of pain alone more than justifies their use.

Bumpus²⁹ is of the opinion that the proof of the greatest good done to the greatest number of patients with carcinoma of the prostate rests with the advocates of radical surgical removal, who as yet have not published lists of survivals in sufficient numbers to be convincing, when their records are compared with equal numbers of patients simply relieved of their obstructions. Now Thompson has come forward with a report that seems to Bumpus to make the position of the advocates of radical operation still more untenable. Thompson showed that after transurethral resection in a series of patients sufficiently large to be convincing statistically, with a mortality of only 1 per cent, 14 per cent lived more than five years. Now that estrogens and castration are available to aid in the treatment of these men, Bumpus predicts that prolonged survivals will be so numerous as to make even the consideration of cure by radical removal with the possibility of mortality and lifelong incontinence seem indeed fantastic. There can be no question about the prolongation of life following castration.

Kearns³⁰ has a series of 42 cases of carcinoma of the prostate, in about 70 per cent of which varying degrees of benefit occurred. All of the results were obtained through the use of estrogens alone. First he used diethylstilbestrol; later ethinylestradiol was used by mouth; still later subcutaneous implantation of alpha estradiol was employed. The last named is the preferred method of administration of estrogen. It is especially applicable for patients who are unable to tolerate either diethylstilbestrol or ethinylestradiol by mouth. It may well be combined with the oral administration of diethylstilbestrol or ethinylestradiol. The one route of administration may be employed to augment the other according to clinical indications.

Vermooten³¹ reports observations on 58 cases of carcinoma of the prostate gland in which bilateral orchiectomies were done. Six years previous to the writing of the report he performed total radical prostatectomy on an old man for carcinoma. Six months previously this patient returned with extensive skeletal and pulmonary metastatic processes but without local recurrence. Before orchiectomy he was extremely dyspneic and practically moribund. Vermooten reports that this patient is once more completely free from metastatic lesions. This makes Vermooten wonder whether radical prostatectomy for even an early lesion is really worth while.

Creedy³² emphasizes the fact that he has advocated radical operation only in the earliest stages. During the period under discussion only 10 radical perineal prostatectomies have been done at the University Hospital (Minneapolis) in a

29. Bumpus, H. C., Jr., in discussion on papers of Alyea and Henderson,²⁴ Creedy,²⁵ Thompson,⁴² Nesbit and Cummings,²⁶ Gutman²⁷ and Herbst,²⁸ *J. A. M. A.* **120**:1120 (Dec. 5) 1942.

30. Kearns, W. M., in discussion on papers of Alyea and Henderson,²⁴ Creedy,²⁵ Thompson,⁴² Nesbit and Cummings,²⁶ Gutman²⁷ and Herbst,²⁸ *J. A. M. A.* **120**:1121 (Dec. 5) 1942.

31. Vermooten, V., in discussion on papers of Alyea and Henderson,²⁴ Creedy,²⁵ Thompson,⁴² Nesbit and Cummings,²⁶ Gutman²⁷ and Herbst,²⁸ *J. A. M. A.* **120**:1121 (Dec. 5) 1942.

32. Creedy, C. D., in discussion on papers of Alyea and Henderson,²⁴ Creedy,²⁵ Thompson,⁴² Nesbit and Cummings,²⁶ Gutman²⁷ and Herbst,²⁸ *J. A. M. A.* **120**:1122 (Dec. 5) 1942.

group of about 500 cases of carcinoma of the prostate gland. All of the patients who had any important obstruction to urination, except for the 10 included in the report, were treated by transurethral resection with or without irradiation. Creevy raises the question as to whether it is justifiable to attempt to cure any sort of cancer of any organ. He does not believe that the general surgeons, despite the low percentages of cures in carcinoma of the stomach or rectum, will concede that one ought to give up, and he still thinks that it is worth while to try for a cure in an appropriate case of early carcinoma of the prostate. He is inclined to hold to that point of view because it will not be known for a long period whether relief from castration or from the estrogens can be counted on. If it is going to be just a flash in the pan, as was castration for inoperable carcinoma of the breast, then Creevy thinks that the availability of the hormone preparations is not a serious argument against radical perineal prostatectomy.

Chute, Willetts and Gens³³ state that reducing the action of androgens in the body was of benefit in 26 of 27 cases of inoperable carcinoma of the prostate gland. The action of androgens was reduced by surgical castration, by biochemical neutralization, by the administration of the synthetic estrogen stilbestrol or by a combination of the two; the last method was used in a majority of the cases (77 per cent).

Beneficial effects in these cases included rapid relief from the pain of metastatic lesions if present, great improvement in appetite and general health with gain in weight and reduction in the size and induration of the prostate with improvement in ability to urinate in most cases.

The injection of 10 mg. of diethylstilbestrol per day for five to ten days augmented the beneficial effects of castration noticeably and rapidly. Similar injections of diethylstilbestrol without castration gave equally noticeable and rapid effects, but these disappeared when its administration was discontinued, whereas the effects of castration, while slower to appear, were permanent. If diethylstilbestrol alone is used, patients have to be given a small oral maintenance dose indefinitely (1 to 3 mg. per day).

Chute, Willetts and Gens feel that the quickest and most satisfactory results in this series were obtained by castration followed by the injection of 10 mg. of diethylstilbestrol per day for five to ten days. Thirteen patients who were suffering from moderate or marked difficulty of urination were treated in this way. The size of the obstructing prostate gland was so reduced in 9 cases that the patients could void freely, did not have much residual urine and escaped having to undergo an operation for the relief of prostatic obstruction. Chute, Willetts and Gens recommend this type of treatment.

No serious harmful effects were noted from the injection of 10 mg. of diethylstilbestrol per day for five to ten days, or from the oral ingestion of 2 to 3 mg. per day over a period of nine months. Unpleasant side effects of treatment with this compound were loss of libido and power of erection, tenderness and hypertrophy of the nipples and breasts, atrophy of the testes and anorexia or occasionally nausea. After castration, libido and power of erection usually disappeared, but there were no other harmful effects.

No beneficial effect was noted on metastatic growths in bone. Roentgenograms taken over a period of more than six months showed them apparently progressing as usual.

33. Chute, R.; Willetts, A. T., and Gens, J. P.: Experiences in the Treatment of Carcinoma of the Prostate with Stilbestrol and with Castration by the Technique of Intracapsular Orchidectomy, *J. Urol.* 48:682-692 (Dec.) 1942

As found by other authors, the concentration of "acid" phosphatase, if elevated, fell rapidly toward normal following castration or administration of diethylstilbestrol, whereas the value for "alkaline" phosphatase usually rose.

Neuswanger³⁴ reported 57 cases of carcinoma of the prostate gland in which treatment consisted of castration and 11 others in which diethylstilbestrol was employed. It has been his experience that the carcinomatous gland recedes in about three to five weeks after operation but that the extracapsular metastatic lesions are affected little or not at all, at least up to the period of twelve months during which time his patients had been under observation.

An interesting result encountered was that of incontinence, which was noticed in 2 cases after castration alone. It is possible that this can be explained by the fact that the sphincter muscle has been weakened by the invasion of the carcinoma and castration causes relaxation and incontinence of urine.

In 1941 Baron and Angrist reported a 10 per cent incidence of occult carcinoma in 364 cases in which random sections of the prostatic tissue were examined at necropsy. In 46 per cent of 50 cases in which a complete study of the gland was done at necropsy following death from causes other than carcinoma of the prostate, they found occult carcinoma.

The untoward results encountered consisted of swelling of the ankles, hot flushes, loss of sexual capacity and tender enlargement of the breasts. The favorable symptoms encountered, which far outweigh the undesirable results, included relief of pain, increase in appetite, gain in strength and weight, improvement in bowel habits and decrease in obstructive symptoms.

Herbst,³⁵ in discussing carcinoma of the prostate gland, states that his observations in twenty-two months' experience have been the same as those just reported except that he employed a smaller dose of estrogen. The reactions observed in the breast have varied from no response at all to gynecomastia (interestingly, in 2 instances unilateral gynecomastia). Estradiol dipropionate was the first estrogenic substance which Herbst used. He has not been able to observe any difference in the response to the administration of estradiol dipropionate and diethylstilbestrol. He states that the only difference so far demonstrated between these substances is the fact that diethylstilbestrol in huge doses is slightly more effective in producing anesthesia in rats than is estradiol.

As time goes on and clinical observations accumulate, certain differences may be recognized in these substances which at present are not apparent. An interesting observation was made on a patient with diabetes who was requiring 12 mg. of protamine zinc insulin daily while being treated with diethylstilbestrol. Since castration, which was done six months previously, he had not required any insulin.

In a microscopic study no changes in cell morphology were observed in 3 instances in which it was possible to study malignant tissue after castration, the administration of diethylstilbestrol, or both. This observation makes it seem unlikely that ordinary microscopic studies will be of much value and that such stains as the Gomori stain will have to be developed so that observations of practical significance may be demonstrated.

The dosage employed in the administration of estradiol dipropionate and diethylstilbestrol was 1 mg. three times a week hypodermically. Recently Herbst has thought that increasing the dose is justifiable and indicated when satisfactory response is not experienced with the 1 mg. dose.

34. Neuswanger, C. H., in discussion on papers of Alyea and Henderson and Chute, Willetts and Gens,³³ *J. Urol.* **48**:694-697 (Dec.) 1942.

35. Herbst, W. P., in discussion on papers of Alyea and Henderson and Chute, Willetts and Gens,³³ *J. Urol.* **48**:697-698 (Dec.) 1942.

Dean³⁶ states that while the final explanation of the cause and prevention of prostatic cancers, if not their cure, will be produced in the chemical laboratory, a prominent part must be played by the urologist, who is a trained observer of the reactions of the test object, the patient. In a group of 40 patients, 15 with metastasis, Alyea found 4 with metastatic lesions in the lung which responded as do secondary deposits in the soft parts elsewhere in the body. In the 60 patients Dean has treated in the past eleven months, no metastasis to the lungs was discovered. After treatment, it is his impression that the patients of Alyea and of Chute and his associates responded in the same spectacular way that so many observed patients have. However, Dean admits that the early benefits of castration were not sustained by as high a proportion of his patients, the majority of whom relapsed after five to six months, nor could he detect as much regression of the primary prostatic tumor and reduction of residual urine after orchiectomy, although the administration of diethylstilbestrol in daily doses of from 3 to 5 mg. produced striking improvement in these respects.

In Dean's experience, after castration the androgen output rose an average of 45 per cent in two thirds of the patients. Assays for estrogen showed decreased excretion in every case. If these analyses represent the true condition of these men, castration should have made them worse, because it appeared to increase markedly their production of androgens relative to estrogens.

Munger,³⁷ in discussing carcinoma of the prostate gland, defends his premise enunciated first in 1934 and again established in a follow-up report presented at Colorado Springs before the American Urological Association in 1941, namely, that carcinoma of the prostate is in some manner related to production of the testicular hormone and that well directed, well planned and properly instituted roentgen therapy applied directly to the testicles will definitely influence that carcinogenic substance, whatever it is, which apparently has its origin in the testicle and seems to be related to carcinoma of the prostate.

The paper presented in Colorado Springs in 1941 was entirely a clinical summation of the procedure as it had been carried on since 1932. After this clinical presentation Munger was rebuffed by certain roentgenologists, pathologists and urologists, whose chief counterargument was that "testicular irradiation has no effect upon the interstitial cells." Munger adds that he is not in a position as yet to state how much organic effect irradiation has on the interstitial cell of the testis, but he says with certainty that if the interstitial cells are the station from which emanates that factor responsible or related to the establishment of carcinoma of the prostate, then roentgen rays do have some effect, basically at least, on the functioning of the interstitial cells. Surgical castration certainly removes the testicle, and thereby the carcinogenic factor within the testicle; diethylstilbestrol does definitely depress this factor within the testicle, and in 85 per cent of cases irradiation seemingly stabilizes or reverses the process. Munger believes all the factors involved are not yet disclosed and that the biochemists may find the answer to this problem.

Sullivan, Gutman and Gutman³⁸ review the theoretic and experimental developments leading to the use of the determination of serum "acid" phosphatase in cases of metastasizing prostatic carcinoma.

36. Dean, A. L., in discussion on papers of Alyea and Henderson and Chute, Willetts and Gens.¹² *J. Urol.* 48:698-699 (Dec.) 1942.

37. Munger, A. D., in discussion on papers of Alyea and Henderson and Chute, Willetts and Gens.¹² *J. Urol.* 48:701-702 (Dec.) 1942.

38. Sullivan, T. J.; Gutman, E. B., and Gutman, A. B.: Theory and Application of the Serum "Acid" Phosphatase Determination in Metastasizing Prostatic Carcinoma: Early Effects on Castration, *J. Urol.* 48:426-458 (Oct.) 1942.

The reliability of the determination as a practical method for the diagnosis of metastasizing prostatic carcinoma is considered on the basis of results obtained in a period of four and a half years of clinical trial. The method failed; that is, values less than 3 units per hundred cubic centimeters were obtained in approximately 15 per cent of 130 cases of prostatic carcinoma and definite or suggestive roentgenographic evidence of metastasis; in the remaining 85 per cent of cases increases in serum "acid" phosphatase occurred, which in extreme instances exceeded 1,000 units per hundred cubic centimeters. Values of less than 3 units per hundred cubic centimeters were obtained in approximately 89 per cent of 70 cases of prostatic carcinoma without roentgenographic evidence of skeletal metastasis, as well as in all of 85 cases of diseases of the prostate gland other than carcinoma. The conclusion drawn from this experience is that the method is consistent and specific enough to be a valuable, though not infallible, supplement to clinical, roentgenographic and other procedures for the diagnosis of metastasizing carcinoma of the prostate gland.

The applications of the determination which have proved useful in diagnosis and treatment are discussed. They include: (1) corroborating the diagnosis of metastasizing prostatic carcinoma when suggested by other methods; (2) providing evidence of metastasis from prostatic carcinoma before it is definitely demonstrable by roentgenologic or other methods; (3) determining the prostatic or nonprostatic origin of tumors in cases of known metastasis; (4) differentiating Paget's disease from metastatic prostatic carcinoma; (5) aiding in the selection of cases for prostatectomy and in the detection of recurrence after prostatectomy, and (6) aiding in the selection of cases in which the disease could be controlled with androgen and in the evaluation and regulation of such treatment. Cases are cited to illustrate these applications.

Castration in 31 cases of metastasizing prostatic carcinoma and serum "acid" phosphatase levels ranging from 520 to 4.2 units per hundred cubic centimeters resulted in an early precipitous fall in serum "acid" phosphatase (often temporarily arrested about the third week by a slight, transient secondary rise, to be followed by a prolonged decline) until at the end of two or three months an equilibrium was reached. The effect of castration on the serum "alkaline" phosphatase was more variable. After a latent period a marked increase in serum "alkaline" phosphatase usually developed, most often about the second or third week, followed by a gradual decline until equilibrium was reached after many months.

Hamm³⁹ states that cancer of the prostate gland is one of the most common forms of cancer. It occurs three times as often in the prostate gland as in any other internal organ in man. Of 316 of Hamm's patients coming to operation for various types of urinary obstruction, 38 (about 12 per cent) had carcinoma.

Adenocarcinoma is the type of cancer most frequently found. In more than half of the cases it is seen in combination with adenomatous hyperplasia, although there is no evidence that the two processes are related. The adenomatous and carcinomatous portions usually overlap.

In some instances metastasis may be extensive even before the neoplasm can be detected by gross inspection of the specimen at necropsy. The most common sites of metastasis are the pelvic girdle and the lumbar vertebrae. Metastasis to bone is predominantly of the osteoplastic type, especially when widespread. When a metastatic lesion of the osteoplastic or mixed type involving the bony pelvis or lumbar vertebrae is found, it is in all probability due to carcinoma of the prostate. In 18 (47.1 per cent) of the 38 operative cases in this study, roentgenographic evidence of metastasis was present at the time of operation.

39. Hamm, F. C.: Clinical Aspects of Carcinoma of the Prostate: Review of Thirty-Eight Operative Cases, *J. Urol.* 48:174-186 (Aug.) 1942.

Advanced carcinoma is characterized by its stony hardness, nodules and a general sensation of being fixed in the pelvis. It is difficult to outline the gland, because its borders seem to merge with the surrounding pelvic structures. There is an obliteration of the median sulcus; the superior margin of the gland may have a shelflike feel so that the examining finger can be hooked over it.

In 6 (15.7 per cent) of Hamm's 38 operative cases there had been no follow-up since operation. Nine patients (23.6 per cent) were traced from three months to three years, but had been lost track of. Fifteen patients (39.5 per cent) were known to be dead. Eight patients (21.05 per cent) have been followed from the date of operation to the present time. Seven of the 8 patients are in excellent health. The ninth patient, who has survived the longest period (five years and eight months) is not well. He has pain extending to the penis and has been advised to undergo orchiectomy.

Riba⁴⁰ discusses subcapsular castration for carcinoma of the prostate gland. The anterior scrotal wall is blocked off with 1 per cent procaine hydrochloride solution. Ten cubic centimeters is then injected directly into each spermatic cord. Each testis may be delivered easily through a 4 to 5 cm. median incision. On the anterior surface both the tunica vaginalis and the tunica albuginea are widely incised. The exposed parenchyma can be easily removed en masse by blunt dissection. The bleeding is minimal. Active bleeders are ligated. Both tunicae are resutured with fine silk. The testis is returned to its bed. The opposite testis is treated likewise through the same incision. The edges of the wound are approximated with interrupted silk sutures or skin clips. The mild intracapsular hemorrhage causes the tunicae to become distended and remain firm, in some instances for many months. The patient is unaware that the total parenchyma is absent. Postoperative mental discomfort is minimized or absent.

Randall⁴¹ reports the results in 5 cases from seven to nine years after castration for carcinoma of the prostate gland. In none of these cases was the malignant process cured. On the other hand, all 5 patients had advanced carcinoma and probably metastasis, and Randall states that failure to obtain a cure may be related to this fact.

Thompson⁴² states that carcinoma of the prostate gland is an insidious disease which usually does not cause symptoms until it is well advanced. It is difficult to detect in its early stages by any known clinical method.

In 95 per cent of cases the disease has spread beyond the confines of the prostate gland when the patients are first observed; in 5 per cent or less, radical perineal prostatectomy may be justified as a method giving hope of cure in the strict sense of the word.

Transurethral resection is the most desirable operation for the relief of obstructive urinary symptoms caused by the disease. Entirely adequate relief for prolonged intervals follows if the operation is properly performed. Normal vesical function is achieved at minimal risk to life and practically no risk of incontinence will result.

Transurethral resection of the obstructing tissue combined with bilateral orchiectomy as suggested by Huggins and the administration of diethylstilbestrol seem to constitute the best method of treatment now available for patients who have reten-

40. Riba, L. W.: Subcapsular Castration for Carcinoma of Prostate, *J. Urol.* **48**:384-387 (Oct.) 1942.

41. Randall, A.: Eight-Year Results of Castration for Cancer of the Prostate, *J. Urol.* **48**:706-709 (Dec.) 1942.

42. Thompson, G. J.: Transurethral Resection of Malignant Lesions of the Prostate Gland, *J. A. M. A.* **120**:1105-1109 (Dec. 5) 1942.

tion of urine. Unless urinary obstruction exists, orchiectomy and diethylstilbestrol therapy seem to constitute the treatment of choice.

Hypertrophy.—Davis,⁴³ in discussing the renaissance of prostatectomy with particular reference to minimal hospitalization without preliminary drainage, states that the urologic surgeon now sees a much larger percentage of "conspicuously good risks," permitting safe prostatic surgery without preliminary drainage. Results obtained in a consecutive series of 24 such cases indicate that the average total period of preoperative and postoperative hospitalization, with good risks, may be reduced to a figure not exceeding sixteen days. This exceedingly short average total hospitalization for perineal prostatectomy tends to nullify the chief argument of those advocating routine or indiscriminate transurethral resection rather than selection of cases. Davis states that this opinion should not be interpreted as blanket approval of prostatectomy without preliminary drainage, the necessity of which will always obtain in cases of impairment of renal function.

Humphreys⁴⁴ reviews the causes of unsatisfactory end results after prostatectomy. After examining the follow-up records of the last 500 prostatectomies in the Cornell Urological Service of the New York Hospital, he found four main causes of unsatisfactory results for which patients had to return for reoperation after prostatectomy in cases in which results still appeared satisfactory six months after operation. The cases were grouped according to these causes.

The commonest cause of poor postoperative results after uncomplicated prostatectomy is persistent urinary infection. In Humphreys' series there were 2 instances of the formation of stones in infected bladders, despite the fact that there was no residual urine. These persistent infections may become less frequent with the advent of the use of sulfonamide compounds. Infections are now being treated routinely with the sulfonamide derivatives and fewer persistent infections are being encountered. If adequate chemotherapy and better follow-up care had been given these two patients, dysuria and formation of stones might have been prevented.

A second cause of unsatisfactory end results after prostatectomy is obstruction of the neck of the bladder due to the formation of scars. Some patients showed delayed healing of urinary sinuses immediately after prostatectomy, owing to the early appearance of scars in the region of the neck of the bladder. They were relieved by transurethral resection. Three of Humphreys' patients and 4 others who had seemingly satisfactory prostatectomies performed elsewhere returned with urinary difficulties due to scars in the form of partial diaphragms at the neck of the bladder. These patients were relieved of their obstructive symptoms by transurethral resection after the vesical neck had been dilated with bougies.

A third cause of unsatisfactory end results after adequate prostatectomy is true recurrence of prostatic hypertrophy. In spite of the difficulties of removing completely all hypertrophic prostatic tissue at operation and in spite of the possibilities of recurrent growth in glandular tubules which remain in the prostatic tissue left, the number of operations for recurrent hypertrophy of prostate glands is small.

Only 2 patients in Humphreys' series of 500 patients operated on for supposedly benign prostatic obstruction returned for subsequent operation because of urinary difficulties resulting from carcinoma of the prostate. Since in both cases treatment for prostatic hypertrophy antedated the second admissions by only three years, it may be assumed that carcinoma of the prostate had been

43. Davis, E.: The Renaissance of Prostatectomy with Particular Reference to Minimal Hospitalization Without Preliminary Drainage, *J. Urol.* **48**:163-169 (Aug.) 1942.

44. Humphreys, G. A.: Some Causes of Unsatisfactory End Results After Prostatectomy, *J. Urol.* **48**:388-391 (Oct.) 1942.

present at the time of the first operations; however, if so, in each case the carcinoma was masked by the symptoms of hypertrophy, the patient was relieved by the removal of the hypertrophied gland and the sections of tissue removed showed no carcinoma.

Female Prostate.—Folsom and O'Brien⁴⁵ discuss the female obstructing prostate. They believe that an infection harbored through the years in the glands surrounding the posterior urethra is the cause of the pathologic picture seen in this portion of the female urethra. From observations, they are convinced that prostatism is a clinical entity that occurs much more frequently in women than is recognized and properly treated. Physicians have so long considered the female prostate as nonexistent that they often fail to ask the proper questions to get an accurate and revealing history.

Clinically these patients present, in addition to irritation of the bladder, some degree of difficulty in voiding. This varies from simply a sense of obstruction and unfinished business on through varying degrees of obstruction to complete retention. Three out of 15 of Folsom and O'Brien's patients had retention.

In 4 cases the vesical urine showed pus to a degree of 4 plus or more, while the specimens of urine collected from the right and left kidneys showed no pus and no organisms. In each of these cases the mucosa of the bladder was not inflamed. Therefore Folsom and O'Brien feel that the condition in these cases is comparable to a similar one in the male, in which the pus originates in the posterior part of the urethra from the prostate and seeps back into the bladder through the relatively weak internal vesical sphincter. A plain cystogram, made with the use of either air or sodium iodide, will frequently reveal a filling defect in the region of the internal orifice similar to the defects seen in men with prostatic hypertrophy. On cystoscopic examination the vesical wall may be normal or grossly trabeculated with cellules and even diverticula and calculi. In the majority of the cases fibromuscular hypertrophy with fibrous hyperplasia and varying grades of inflammatory reaction are present. In some cases actual gland structures have been reported, and these seem to be identical with similar lesions in the male.

Folsom and O'Brien are of the opinion that the most plausible explanation for the pathologic lesion under discussion is, first, that there is a homologous group of glands surrounding the posterior part of the female urethra and, second, that these glands do become infected and that after they have harbored this infection for months or years bars, collarets and cicatricial contractions are produced.

In performing transurethral resection in the female one must be much more careful in technic than in operating on the male: first, for the simple reason that in dealing with miniature prostates it is necessary to be more sparing in the bites of tissue removed to insure against cutting through the urethrovaginal septum; second, for the reason that there is not, as far as has been observed, a capsule that may be seen during resection and hence act as a guide; third, because excessive fulguration may be as bad as too deep a cut. As little fulguration as possible should be used and the Foley bag and traction should be relied on to control the bleeding.

In 5 of Folsom and O'Brien's cases the resection was limited to the lower segment of the urethral circumference, since they were in these cases dealing with a bar. In 9 cases the entire circumference of the urethra was resected. It was necessary to resect the upper segment in 1 of these cases, in which no result was obtained after the first resection, which was limited to the lower segment.

45. Folsom, A. I., and O'Brien, H. A.: The Female Obstructing Prostate. *J. A. M. A.* 121:573-580 (Feb. 20) 1943.

Only 1 death occurred after resection in this series of cases, that of a woman aged 67 years who had rather severe diabetes and myocardial damage resulting from a previous coronary occlusion.

Nesbit⁴⁶ states that in the reported cases of prostatism in women in which relief has been brought about by transurethral resection three definite objective findings have been of value in diagnosis: first, residual urine; second, trabeculation of the bladder and, third, a palpable lesion which can be seen with the aid of a cystoscope or a urethroscope. During the past year, Nesbit has seen 2 women whose cases might fall into this category. They had difficulty with urination. One of them had complete retention of the urine requiring catheterization. Neurologic examination gave negative results in both cases. In both there was residual urine. There was a moderate degree of trabeculation, and on pantoscopic examination a visible bar was present which was not palpable by vaginal examination on the instrument. In these 2 cases, it was suspected that neurogenic contraction of the vesical outlet or the internal sphincter might have been present. In order to differentiate this point, a local anesthetic agent was injected into the lumbar sympathetic nerves. One can tell whether this injection is taking hold, because immediately the patient's legs get an increase in warmth. In both cases the visible contracture of the vesical outlet disappeared on cystoscopy, and Nesbit was saved the embarrassment of having operated on a functional rather than an organic bar, which is something to hold in mind. Residual urine, trabeculation of the bladder and a palpable lesion are important.

Kretschmer⁴⁷ states that obstruction at the neck of the bladder in both children and adult females is a rare lesion. However, it occurs more frequently than is generally recognized. Many girls and women with trabeculation and hydronephrosis have as the underlying cause obstruction at the neck of the bladder. This condition is frequently overlooked, and as a rule the patients when consulting the physician come in late in the course of the disease, after irreparable damage to the upper part of the urinary tract has occurred. Therefore it behooves all to be on the lookout for such obstruction and to remove it before damage to the upper part of the urinary tract has taken place. Kretschmer agrees with Folsom and O'Brien that the treatment is transurethral resection. He has had most satisfactory results.

O'Connor⁴⁸ states that he has encountered 9 women with unmistakable mechanical obstruction of the vesical neck. Folsom and O'Brien have had the opportunity of studying Kodachrome photomicrographs of the tissue removed by transurethral resection from these 9 patients. The obstructing tissues removed from the patients O'Connor has seen has not been uniform. Some of these tissues were purely fibromuscular, some were granulomatous or inflammatory and some had a predominance of glandular elements. O'Connor agrees that the term "prostatism" as applied to women is misleading. Patients with this condition must not be confused with the hermaphrodites or pseudohermaphrodites who actually appear to be female yet have male gonadal tissue. Before resection of an apparent obstruction at the neck of the bladder in women, it is imperative that the part which relaxation of the floor of the bladder plays be recognized. In cystocele, moderate or advanced, cystoscopic examination often reveals an apparent increase in the size of the internal sphincter or vesical neck. The neurologic examination must be negative, there must be both visual and palpable tissue apparently

46. Nesbit, R., in discussion on Folsom and O'Brien.⁴⁵

47. Kretschmer, H. L., in discussion on Folsom and O'Brien.⁴⁵

48. O'Connor, V. J., in discussion on Folsom and O'Brien.⁴⁵

obstructive in character and there must be residual urine that cannot be explained by relaxation of the floor of the bladder before the indications are clear for trans-urethral resection of the vesical neck of the female.

TESTICLES

Tumor.—Gilbert⁴⁹ reviews 60 cases of pseudohermaphroditism with testicular tumors and presents 1 additional case, making a total of 61 cases. This group is approximately 1.0 per cent of 5,516 cases of testicular tumor studied in detail. The pathologic types in the neoplasms studied consisted of 38 unicellular tumors (seminoma; 62.2 per cent); 14 teratomas (22.6 per cent) and 9 miscellaneous or "malignant" tumors (14.7 per cent). Two tumors were located in the scrotal testis, 8 in the inguinally retained testis and 48 in the abdominally retained testis. Neither the side nor the site of the remaining 3 growths was stated in the reports. In 8 cases both gonads were involved. In 41 cases the lesion was considered operable. Operation was performed in 11 cases in spite of metastasis, while the lesions in the remaining 9 were considered inoperable. Four patients survived 5 years or more, 3 of whom had unicellular tumors and 1 a teratoma.

Reports of the 8 cases of bilateral testicular tumor are given in abstract form because of their importance in the study of paired organs. The pathologic types in this group were unicellular tumors in 4 cases, teratomas in 3 and adenoma in 1 case.

In only 4 cases were Aschheim-Zondek assays carried out, and all failed to show the presence of any choriogenic hormone. In all 4 cases unicellular tumors were present. No assays for estrogen or androgen were made.

Three of the 52 noninvolved gonads were located in the scrotum, 1 in the perineum, 8 in the inguinal region and 38 in the abdomen. In 2 instances the site was not stated. Inguinal hernia was present in 12 cases (19.7 per cent). The presence of hernia may be the only lead to the identification of pseudohermaphroditism.

Dockerty and Priestley⁵⁰ state that tumors of the testicle are relatively infrequent, occurring only once in approximately every 1,500 males admitted to larger clinics. Ninety-five per cent of these tumors are malignant, with seminoma and carcinomatous teratoma sharing an almost equal incidence. Sarcoma, for some strange reason, is rarely observed in the testis. The authors present the clinical and pathologic data in 4 cases of lymphosarcoma of the testicle. Whereas earlier cases of seminoma had been mistaken for lymphosarcoma, modern cytologic studies combined with a more or less characteristic cellular infiltration about recognizable seminiferous tubules furnished the criteria for accurate differentiation. Involvement of the skin and of lymph nodes was observed and interpreted as evidence that the testicular lesion was metastatic and not primary, since the nodule in the testicle sometimes appeared as a late manifestation. A high incidence of bilateral involvement (50 per cent) was similarly interpreted. The only other metastatic malignant lesion Dockerty and Priestley could find in a series of 400 testicular tumors was a melanoepithelioma. Thus lymphosarcoma of the testicle, however rare, represented the majority of metastatic malignant processes involving the testicle.

49. Gilbert, J. B.: Studies in Malignant Testis Tumors: VIII. Tumors in Pseudohermaphrodites; Review of Sixty Cases and a Case Report, *J. Urol.* **48**:665-672 (Dec.) 1942.

50. Dockerty, M. B., and Priestley, J. T.: Lymphosarcoma of the Testis (Report of Four New Cases), *J. Urol.* **48**:514-523 (Nov.) 1942.

Prince⁵¹ reports 2 cases of rhabdomyosarcoma of the testicle. One of the tumors was a highly undifferentiated growth, without demonstrable elements to prove its teratomatous nature. The other was a fairly well differentiated growth showing, in addition to the predominating rhabdomyosarcoma, areas of embryonal carcinoma, adenocarcinoma and papillary adenocarcinoma, with benign structures derived from all three germ layers.

Dermoid Cysts.—Dockerty and Priestley⁵² report 3 cases of dermoid cysts of the testicle. Although primary testicular tumors occur in approximately 1 of every 1,500 males admitted to the Mayo Clinic, dermoid cysts constituted less than 1 per cent of testicular tumors. The tumors reported were slow growing and benign. In 1 case the history indicated a congenital injury. In 1 case stratified squamous cells without any specialized epithelial structures made up the cyst wall, while in 2 cases all three germ layers were represented although ectoderm and its derivatives were predominant. Orchiectomy was performed in all 3 cases.

EPIDIDYMIS

Tumors.—Gordon-Taylor and Ommaney-Davis⁵³ state that tumors of the epididymis are the least frequent of all neoplasms.

They report a case of adenoma of the epididymis. The patient, a young man, had swelling in the left side of the scrotum. Examination revealed a painless enlargement of the testicle. The epididymis apparently was not selectively involved, and a diagnosis of tumor of the testicle was made. Castration was carried out, and examination revealed an encapsulated, rounded tumor of the epididymis separate from the testicle. Microscopic examination revealed the growth to be an adenoma.

Blumer and Edwards⁵⁴ report a case of adenoma of the epididymis. Their patient was a man 54 years of age. He had a hydrocele which had been tapped a year previously. He stated that he had a stone in his scrotum which had been present since he was a boy. A radical operation for hydrocele was performed, and a small, rounded hard mass was discovered in the lower end of the testicle. The mass was removed by blunt dissection; it was completely and easily separated from the testicle and epididymis, which appeared quite healthy, but on histologic examination the lesion was found to be an adenoma of the epididymis.

Strong⁵⁵ discusses tumor of the epididymis and reports the case of a man aged 38 years who had a nodule in the region of the right testicle which was noticed first five years before examination. The tumor was about 1 cm. in diameter and caused little trouble. Examination showed the lower pole of the right epididymis to be enlarged, smooth and firm, adherent to the testicle but not to the skin. The proximal 4 to 5 cm. of the vas was somewhat nodular. Epididymectomy and partial vasectomy on the right side, with removal of a small amount of normal testicular tissue, was carried out. Histologic examination revealed the tumor to be a rhabdomyosarcoma. Strong states that this is probably the first recorded instance of such a primary epididymal tumor.

51. Prince, C. L.: Rhabdomyosarcoma of the Testicle, *J. Urol.* **48**:187-195 (Aug.) 1942.

52. Dockerty, M. B., and Priestley, J. T.: Dermoid Cysts of the Testis, *J. Urol.* **48**:392-400 (Oct.) 1942.

53. Gordon-Taylor, G., and Ommaney-Davis, C.: A Case of Adenoma of the Epididymis with a Note on Solid Tumors of the Epididymis, *Brit. J. Surg.* **29**:260-262 (Oct.) 1941.

54. Blumer, C. E. M., and Edwards, J. L.: Adenoma of the Epididymis, *Brit. J. Surg.* **29**:263-265 (Oct.) 1941.

55. Strong, G. H.: Primary Malignant Tumor of the Epididymis (Rhabdomyosarcoma), *J. Urol.* **48**:533-535 (Nov.) 1942.

SPERMATIC CORD

Tumor.—Strong⁵⁶ states that involvement of the spermatic cord by neoplasm is an uncommon but not rare occurrence. To date, 257 tumors have been reported, of which 64 per cent were benign. Malignant tumors appearing in the spermatic cord have been predominantly sarcomatous. He records a case of lipomyxoma of the spermatic cord and 5 additional cases of tumors of the spermatic cord.

Marshall⁵⁷ reports a case of tumor of the spermatic cord. The patient, a man 62 years of age, had a mass in the left side of the scrotum for eighteen months. The mass was removed entirely, and at the time of the operation it was demonstrated that this did not arise in connection with a hernia, the tunica vaginalis, the epididymis or the testicle. The growth was composed of three closely related neoplasms, each distinct, grossly and histologically.

URETHRA

Rupture.—Silverstone⁵⁸ states that ruptures of the urethra usually occur in the male. Ruptures may be complete, involving the whole circumference or incomplete, involving a segment only or the mucosa only.

Treatment of ruptures of the urethra is by no means standardized. The majority of surgeons subscribe to certain principles of treatment: (1) diversion of the urine from the traumatized region; (2) reconstruction of the urethral channel; (3) maintenance of the caliber of the urethra during healing and during a variable postoperative period.

Many surgeons still deal with a complete rupture of the anterior portion of the urethra by perineal operation only. There is no doubt that preliminary suprapubic cystostomy renders the finding of the proximal end of the urethra a simple matter. Except when suture is impossible, it is not necessary to leave a catheter as a splint. When urine drains along the catheter, urethritis is inevitable and formation of stricture likely.

Rupture of the urethra should be dealt with at the time of injury. To postpone this until a later date would be to subject the patient to a second operation, perineal section with excision of scar tissue and repair of the urethra, which could always be done for stricture of the urethra if it had formed as a result of the primary operation. It is further suggested that suprapubic cystostomy, which helps with the localization of the proximal end of the urethra, then should be used for the purpose of diversion of the urinary stream.

TREATMENT WITH SULFONAMIDE COMPOUNDS

Finland, Peterson and Goodwin⁵⁹ report the results of treatment with sulfadiazine in 460 cases of a variety of infections. The earlier conclusion (at which time 446 other cases were reported) concerning the efficacy and low toxicity of sulfadiazine has been confirmed and extended.

The additional data which these authors present suggest that sulfadiazine may be accepted as the drug of choice in all cases of hemolytic streptococcal infections and for all of the various acute bacterial meningitides.

56. Strong, G. H.: Lipomyxoma of the Spermatic Cord: Case Report and Review of Literature, *J. Urol.* **48**:527-532 (Nov.) 1942.

57. Marshall, V. F.: Tumor of Spermatic Cord: Report of Case, *J. Urol.* **48**:524-526 (Nov.) 1942.

58. Silverstone, M.: Traumatic Rupture of the Urethra, *Brit. J. Surg.* **30**:70-74 (July) 1942.

59. Finland, M.; Peterson, O. L., and Goodwin, R. A., Jr.: Sulfadiazine: Further Clinical Studies of Its Efficacy and Toxic Effects in Four Hundred and Sixty Patients, *Ann. Int. Med.* **17**:920-934 (Dec.) 1942.

The accumulated clinical results in the cases of acute gonococcic and staphylococcic infections and of acute infections of the urinary tract suggest that the efficacy of sulfadiazine in most cases of such infections is probably similar to that of sulfathiazole. Because of its lower toxicity, however, sulfadiazine may be considered to be the drug of choice, particularly when prolonged therapy is desirable.

Toxic effects attributable to sulfadiazine in this series were relatively few and mild. The comparatively frequent occurrence of complications in the urinary tract warrants the exercise of caution in the control of the dosage of the drug in relation to the intake and output of fluid. Caution is particularly essential for old persons, for patients with hypertension and for every patient who may have some impairment of renal function. With adequate control, this drug may be administered so that it produces therapeutically effective blood levels whenever indicated, even in many cases of severe renal disease. When oliguria occurs, the intake of fluid should be increased promptly or the dose of the drug reduced, depending on the circumstances. When there is marked or complete suppression of the output of urine, particularly if this is accompanied by ureteral pain, fluids should be forced and ureteral catheterization should be employed early if a fatal outcome is to be avoided. A fatal case of urinary suppression with ureteral colic, hematuria and azotemia is reported.

The occurrence of granulocytopenia after prolonged therapy in 1 case suggests that, regardless of how infrequent this complication may be, it must be looked for in all patients undergoing treatment with sulfadiazine for two weeks or more. Early recognition, with prompt withdrawal of the drug, will probably prevent fatalities from this complication.

Full courses of sulfadiazine were used for a considerable number of patients who previously had been treated with other sulfonamide compounds. The toxic effects from sulfadiazine in these cases were apparently similar in frequency and in all other respects to those encountered in cases in which there had not been any previous experience with other sulfonamide compounds. This was true regardless of whether or not the other drugs had produced toxic effects.

No evidence of "sensitization" was noted in any of the 21 cases in which a second or third course of sulfadiazine was given. In most of these cases full doses were used for a week or more each time. In some of them one or more courses of other sulfonamide drugs had been given also, with or without toxic effects. The possibility of sensitization, however, has not been excluded.

Greene, Pool and Cook⁶⁰ gave sulfadiazine in 42 clinical cases of infections of the urinary tract of varying degree due to a number of organisms in order to compare the drug with the other commonly used sulfonamide compounds. Fifty-seven per cent of the group of patients were considered cured and 29 per cent improved; 14 per cent were not improved and the results were classed as failures. The drug was of little value in the presence of urinary calculi, urinary retention or deep-seated pathologic changes. The results in the treatment of gonorrhea were promising. Approximately 3 Gm. of the drug was given daily in divided doses. The disagreeable side effects noted were less frequent and less severe than those which occur when the other sulfonamide compounds are employed. These authors are of the opinion that sulfadiazine is slightly less effective and more expensive but less toxic than sulfathiazole.

60. Greene, L. F.; Pool, T. L., and Cook, E. N.: Sulfadiazine in the Treatment of Infections of the Urinary Tract, *Proc. Staff Meet., Mayo Clin.* **17**:510-511 (Sept. 23) 1942.

Wright and Kinsey⁶¹ report that 7 of 38 patients given sulfadiazine had renal complications. The amount of the drug, the concentration in the blood, the duration of the therapy, the intake of fluid and the urinary output are not the only factors involved in renal complications from sulfadiazine therapy. The urinary output was relatively low in comparison with the intake of fluid in the cases studied. This was one of the most constant findings in the 7 cases in which complications occurred. Renal tenderness was present in all 7 cases of renal complications and may prove a valuable warning sign. The finding of even a few erythrocytes, with or without crystals, in the urine is an indication that the drug should be withdrawn. There are probably two types of renal damage, one due to mechanical blockage and the other similar to poisoning from mercury bichloride. In most cases renal complications from sulfadiazine therapy will respond to conservative measures if they are instituted early. The purpose of these comments is not to decry the use of this valuable therapeutic agent but to emphasize the assiduous vigilance that is necessary to assure the safety of its use, particularly in the torrid climates and during the hot summer months in the temperate zone.

Louria and Solomon⁶² report a case of anuria caused by sulfadiazine. The patient was a woman aged 25 years who had rheumatic heart disease. Therapy consisted of administration of sulfapyridine for twenty-four hours and later sulfadiazine. After five days of apparent tolerance to sulfadiazine, during which time there was no effect on the fever, the patient voided only 150 cc. of urine. Use of the drug was stopped immediately, but complete anuria was present all through the following day. The concentration of the drug in the blood on the day that its use was discontinued was 22.4 mg. per hundred cubic centimeters. A crystalline deposit was seen in the right ureteral orifice at cystoscopy. After irrigation of the right renal pelvis with warm saline solution, a slight, moderately active flow of urine appeared. Irrigation of the left renal pelvis with warm saline solution was necessary also to obtain a flow of urine. The catheters on both sides were left in place for seventy hours. These authors conclude that if the output of urine is good the presence of crystals in the voided urine should not be considered an indication for discontinuing use of the drug. The appearance of gross blood in the urine at any time during administration of the drug should be an indication for discontinuing its use. Hematuria clears up promptly after administration of the drug has been stopped. No permanent renal damage has been observed in the cases in which recovery has been reported. Obstruction of the urinary tract resulting from the deposition of crystals of the drug may be relieved promptly by ureteral catheterization and pelvic lavage. Whether alkalization of the urine will prevent deposition of crystals in the urinary tract is still a moot point.

Greenwald⁶³ reviews the cases of patients with chancroidal infection admitted to the genitourinary disease service, Station Hospital, Fort Belvoir, Va., during a period of nine months.

Usually an incubation period of three to twelve days elapses before the onset of the ulcerations. Clinically, chancroid infection manifests itself as irregular, nonindurated ulcers with a granular, dirty grayish base, covered with a small amount of grayish purulent discharge. The edges are slightly undermined and irregular. The base bleeds easily on manipulation. Most of the chancroidal ulcers

61. Wright, D. O., and Kinsey, R. E.: Renal Complications Due to Sulfadiazine, *J. A. M. A.* **120**:1351-1354 (Dec. 26) 1942.

62. Louria, A. L., and Solomon, C.: Complete Anuria Caused by Sulfadiazine, *J. A. M. A.* **120**:1354-1356 (Dec. 26) 1942.

63. Greenwald, E.: Chancroidal Infection, *J. A. M. A.* **121**:9-11 (Jan. 2) 1943.

appear at the edge of a phimotic prepuce or, in circumcised males, on the frenum and in the coronal sulcus.

In this series Greenwald has found a chancroidal lesion coincident with syphilis in 10 instances. These cases presented no problem in therapy, however, for no adverse reaction marked the simultaneous use of sulfathiazole and daily full doses of mapharsen as used in the treatment of primary syphilis.

Once the diagnosis of Ducrey infection is made, Greenwald's routine consists in the administration of sulfathiazole in 4 Gm. daily doses, the initial dose being 2 Gm. These doses of the drug are continued for a minimum of seven days, with careful observation for toxic phenomena. In no case in this series was there indication for withdrawal of the drug because of toxicity. After a minimum of four dark field examinations, with negative results, in the intervals between which local application of dressings wet with saline solution was used, the lesions were treated twice daily with soaks in 1 : 8,000 potassium permanganate solution followed by application of sulfanilamide powder.

Helmholz⁶⁴ studied the effect of the commonly used sulfonamide compounds, namely, sulfathiazole, sulfadiazine, sulfacetimide (acetylsulfanilamide) and sulfapyridine, on a large number of strains of the bacteria isolated from urinary infections. Sulfathiazole acts bacteriostatically in lower concentrations (0.5 to 2.0 mg. per hundred cubic centimeters) than the other three compounds on the most frequently found organism, *Escherichia coli*. Except in the case of one resistant strain, sulfadiazine, sulfacetimide and sulfapyridine in concentrations of 50 mg. per hundred cubic centimeters completely inhibited the growth of *Staphylococcus aureus*. Of the 5 organisms studied with varying concentrations of the sulfonamide compounds, *Pseudomonas aeruginosa* was found to be the most resistant, followed in order by *Proteus ammoniae*, *Staphylococcus aureus*, *Aerobacter aerogenes* and various strains of *Salmonella*. Sulfapyridine did not exhibit the bacteriostatic properties of the other sulfonamide compounds and sulfathiazole was superior to the others in lower concentrations. Sulfathiazole seems to have the greater bacteriostatic action on a mixture of organisms.

Loveless and Denton⁶⁵ discuss the oral use of sulfathiazole in prophylaxis for gonorrhea. Sulfathiazole was given in doses of 2 Gm. as a prophylactic measure to a company of 1,400 Negroes before they left the fort on pass. Those taking station prophylaxis received no further drug. All others received an additional 4 Gm., 2 on returning to the fort and 2 the next morning. In this company a phenomenal disappearance of gonorrhea and chancroid occurred. If the men for whom this prophylactic measure failed who were not under the influence of the drug at the time of exposure are excluded, the gonorrhea rate dropped to a level of 8 per thousand yearly, as compared with 171 per thousand in the control group, and the chancroid rate dropped to 6, as compared with 52 in the control group.

UROLOGIC SURGERY

Priestley, Walters and Counseller⁶⁶ gave a report of urologic surgery carried out at the Mayo Clinic in 1941. In the entire group of 956 patients who were

64. Helmholz, H. F.: The Bacteriostatic Action of Sulfadiazine, Sulfathiazole, Sulfacetimide and Sulfapyridine on Bacteria Isolated from Urinary Infections, *Proc. Staff Meet., Mayo Clin.* **17**:529-533 (Oct. 21) 1942.

65. Loveless, J. A., and Denton, W.: The Oral Use of Sulfathiazole as a Prophylaxis for Gonorrhea, *J. A. M. A.* **121**:827-828 (March 13) 1943.

66. Priestley, J. T.; Walters, W., and Counseller, V. S.: Report of Urologic Surgery for 1941, *Proc. Staff Meet., Mayo Clin.* **17**:603-605 (Dec. 16) 1942.

treated surgically, only 6 deaths occurred, a mortality rate of 0.6 per cent. This is the most favorable mortality rate ever attained at the Mayo Clinic in the care of these patients. Many factors undoubtedly contributed to this mortality rate, including improvements in preoperative and postoperative care.

Of the various operations performed in 1941, operations were performed on the kidney in 334 cases with 5 deaths, a mortality rate of 1.5 per cent. In the majority of surgical cases of nephrolithiasis a conservative operation was performed, as nephrectomy is necessary in only approximately 1 of 4 of these cases. This is in contrast with the surgical cases of hydronephrosis, as in this group nephrectomy was performed in approximately 2 of 3 cases. During the past five years hydronephrosis has been treated surgically in 246 cases with no deaths. Renal tuberculosis was seen much less commonly in 1941 than in former years. Malignant tumors of the kidney compose an important group of lesions for which nephrectomy is required. Virtually all solid renal neoplasms of clinical significance are malignant. Approximately 80 per cent are adenocarcinomas or hypernephromas, 9 per cent epitheliomas, 5 per cent sarcomas, 5 per cent Wilms tumors and the remainder unusual types of lesions. During 1941 nephrectomy was performed in a total of 204 cases with 2 deaths. During 1941, according to Priestley and his associates, operations on the ureter were performed in 73 cases with 1 death at the Mayo Clinic. Ureterolithotomy was performed in 36 cases, and 1 death occurred in this group. Cases in which ureteral transplantation has been required have been of particular interest. During 1941 bilateral ureterosigmoidostomy was performed in 22 cases without a death. In 15 of these cases simultaneous bilateral ureterosigmoidostomy was carried out. During the past few years, several things have been learned regarding ureteral transplantation: (1) that proper preoperative preparation and postoperative care are extremely important; (2) that both ureters can be transplanted simultaneously without undue hazard, and (3) that the grossly abnormal ureter can be transplanted to the bowel in most instances with reasonable safety. In 11 of the 22 cases of bilateral ureterosigmoidostomy, carcinoma of the bladder was present. Cutaneous ureterotomy is an operation which is used infrequently and never from choice. In an exceptional case of advanced or complicated renal tuberculosis it may find a field of usefulness.

Surgical treatment of vesical lesions during 1941 was followed by results more gratifying than usual as 59 patients were operated on without a death. Twenty-seven of these 59 patients had malignant tumors. In 11 cases total cystectomy preceded by bilateral ureterosigmoidostomy was performed without a death. In 13 cases segmental resection of the bladder was carried out. During recent years interest in total cystectomy has grown materially. Priestley and his associates are of the opinion that as indications for treatment, preoperative preparation, surgical technic and postoperative care of vesical lesions become more standardized and thoroughly understood, indications for total cystectomy will become even broader. At present it is established that this procedure can be carried out with reasonable risk, and if cases are properly selected the ultimate prognosis should be more favorable than that associated with any other form of treatment for similar types of vesical carcinoma.

During 1941 orchidectomy was performed in 25 cases of carcinoma of the prostate gland. Priestley and his associates think that this form of treatment for prostatic carcinoma, suggested during recent years by Huggins, gives promise of being a great advance in the management of this condition. No patient had suprapubic or perineal operation for prostatic hypertrophy. During this same interval Thompson and his associates performed transurethral resection in 991 cases.

Eighty patients were treated for embryologic defects of the external genitalia, and testicular tumors were removed from 18.

Thompson, Emmett, Cook and Pool,⁶⁷ in discussing transurethral surgery at the Mayo Clinic in 1940 and 1941, state that in 1941 991 patients were subjected to transurethral resection of the prostate gland. Improvements in instruments and in technic, which have made it possible to apply the operation to many patients who were formerly denied relief of obstructive urinary symptoms, account in part for the increased number of patients coming to operation. The universal application of transurethral prostatic resection is indicated by the fact that during 1941 not a single patient was treated by perineal or suprapubic prostatectomy at the clinic.

The average age of the patients in this series was 66.2 years. Eighty-five (4.3 per cent) were 80 years of age or older. Only 2 of the patients who were in their eighties died after operation, a fact which attests to the relative safety of the procedure. The great majority of the patients left the hospital on the fifth or sixth postoperative day or before that time. Review of the records showed that of the 1,967 patients undergoing prostatic operation in the last two years (1940 and 1941) only 13 (less than 1 per cent) required more than one month of hospitalization after the operation. The average postoperative stay of the entire group was seven and seven-tenths days.

The average amount of tissue resected has steadily increased throughout the past decade, so that in 1941, if cases in which the obstruction was caused by a bar or contracture are excluded, the average weight of tissue removed was 37.3 Gm. per case. More than 100 Gm. was resected in 9 cases (1 per cent). In both 1940 and 1941, one stage transurethral resection was done in more than 96 per cent of cases.

Prior to ten years ago, suprapubic cystostomy was a commonly used method of preparing patients for subsequent removal of the prostate gland. Thompson and his associates have long felt that with proper catheter technic almost any patient with disease of the prostate could be prepared for operation by drainage of the bladder through a urethral catheter. They state that this does not necessarily mean that an inlying catheter is always used. It is often good judgment to utilize intermittent catheterization or go ahead with the operation without preliminary vesical drainage of any type. The reasons for making the decision as to the type of pre-operative treatment were considered too involved to include in their article. However, it is of interest that in not a single case in the two years was suprapubic cystostomy done prior to operation as the means of treating a patient who had renal insufficiency or who was intolerant to urethral drainage with a catheter.

Litholapaxy either with or without prostatic resection was performed in 131 cases in the two years. Thompson and his associates prefer to use the Bigelow type of lithotrite and evacuate the fragments through a large direct vision cystoscope.

Treatment of tumors of the bladder at the Mayo Clinic has been somewhat altered during the past two years, in that Priestley, Walters and Counseller have done a number of total cystectomies on patients suffering from tumors of a high grade of malignancy. In the majority of cases, however, particularly in cases of vesical tumors of low grade, transurethral removal has seemed to be the method of choice. It was used in 333 instances. Since multiple sittings were employed in some cases, this does not represent the number of patients. However, tumors were presumably completely removed by transurethral means in 139 cases in the two

67. Thompson, G. J.; Emmett, J. L.; Cook, E. N., and Pool, T. L.: Transurethral Surgery in 1940 and 1941, *Proc. Staff Meet., Mayo Clin.* 17:621-624 (Dec. 30) 1942.

years. In many of these the growths were of a low grade papillary nature, and in relatively few cases were tumors of high grade malignancy thus treated. In 18 of the latter cases radon emanation seeds were implanted.

Removal of ureteral calculi by transurethral manipulation was attempted in 150 cases by Thompson and his associates in 1940 and 1941. They state that success in removal of ureteral calculi depends on a number of factors and that good judgment as to the management of any patient results only from considerable experience. Even then discouraging and disappointing results sometimes ensue after any type of manipulation in what should be an easy operation. Successful results were obtained in 95 per cent of 150 cases. In several cases rather sharp postoperative reactions complicated the procedure. The Councill and Johnson stone extractors were employed in the large majority of cases, and as a rule the stone was removed at the time of manipulation. To guard against reaction, urethral drainage with a catheter, as well as drainage of the bladder with a urethral catheter, was employed for the first two or three days after manipulation.

The mortality rate following transurethral prostatic resection is of considerable interest. In 1940 there were 16 deaths among 976 patients, or a mortality rate of 1.6 per cent. In 1941 there were 11 deaths among 991 patients, or a rate of 1.1 per cent.

Colby⁶⁸ reports cutaneous ureterostomy in 10 cases of active renal tuberculosis. Advanced disease was present in all cases. In many there was active tuberculosis of bone, genital lesions and probably other areas of unsuspected disease, although there were no active pulmonary lesions. Cutaneous ureterostomy entails little risk; no deaths resulted directly from the operation, although 1 patient died from a ruptured tuberculous ulcer of the small intestine before leaving the hospital. Simultaneous bilateral ureterostomy was done on 2 patients who had tuberculosis of both kidneys. Both died within a few months, and neither was particularly benefited while alive. Considerable benefit from the operation results in those patients whose remaining kidney was diseased after the removal of the opposite tuberculous kidney. With them intolerable symptoms referable to the bladder were relieved and the progress of renal damage lessened. Five such patients who were treated by ureterostomy are alive and useful. If the operative result is a rosette of ureteral mucous membrane projecting beyond the skin, there is reason to believe patients can live comfortably without catheters and that they may escape formation of stricture at the skin, even in the presence of active renal tuberculosis. If this is true, these patients can easily care for themselves without the nuisance of changing catheters, and the danger of pyelonephritis, secondary infections with urea-splitting bacteria and formation of stones is lessened. Cutaneous ureterostomy, as usually performed, holds no guarantee of a satisfactory junction of skin and ureter. It is the most effective method of relieving symptoms from the hopelessly infected tuberculous bladder.

UROLITHIASIS

Jewett, Sloan and Strong⁶⁹ discuss vitamin A deficiency and clinical urolithiasis. The rate of dark adaptation and the thresholds of the completely dark-adapted eye were determined for 20 patients with urolithiasis and compared with those of 40 normal subjects. In addition the vitamin A content in the blood of these patients with urolithiasis was determined and compared with that of 33 normal

⁶⁸ Colby, F. H.: Cutaneous Ureterostomy in Active Renal Tuberculosis, *J Urol.* **48**: 357-367 (Oct.) 1942.

⁶⁹ Jewett, H. J.; Sloan, L. L., and Strong, G. H.: Does Vitamin A Deficiency Exist in Clinical Urolithiasis? A Clinical and Pathologic Study of Ninety-Eight Cases, *J. A. M. A.* **121**:566-568 (Feb 20) 1943

control subjects. In 78 cases of urolithiasis which came to necropsy the respiratory and urinary tracts were examined for the epithelial metaplasia characteristic of vitamin A deficiency. In none of the 98 cases studied was there any evidence of vitamin A deficiency. Although a vitamin A-free diet produces widespread epithelial changes which may lead to the formation of urinary calculi in experimental animals, as yet there is no positive proof that "subclinical" vitamin A deficiency is an etiologic factor in urolithiasis in man.

Flocks⁷⁰ reviewed the material at the University Hospitals (Iowa City) and found that there was no evidence of vitamin A deficiency as an associated factor in 100 cases of calcium urolithiasis. This tends to confirm the careful work of Jewett who has proved conclusively that in cases of calcium urolithiasis there is no more vitamin A deficiency than in any comparable group of cases of some other disease. Flocks is in doubt as to whether the problem had been completely cleared up, in view of the fact that in most of the cases of stone in the urinary tract the picture that is seen at the time the patient is observed is an end result. It is not the picture at the time when the stone is actually forming, and it may well be that when the stone or nucleus started one of the initiating factors was vitamin A deficiency. This fits in with some of the experimental work done on animals. It fits in with the known rapid formation of small calculi in acutely ill, bedridden, vitamin-deficient persons. The further growth of these stones, however, has no relation to vitamin A deficiency, as Jewett and his co-workers have conclusively proved. Whether or not vitamin A deficiency is an important associated factor in the formation of the nucleus is, Flocks believes, still a question which can be answered only by providing some means of demonstrating whether or not the patients are deficient in vitamin A during the time of formation of the nucleus.

DISSOLUTION OF URINARY CALCULI

Suby, Suby and Albright⁷¹ discuss the property of acid solutions in relation to irritability of the mucosa of the bladder. Rabbits were used in their experimental work. In all, about 80 tests were carried out on the bladders of rabbits with the various solutions. Physiologic solution of sodium chloride was used for the test solution, and in none of these tests was any bleeding evident in the outflowing solution. After the use of sodium citrate-citric acid solution, the returning fluid was slightly pink. The addition of magnesium to the sodium citrate-citric acid solution eliminated the irritability without reducing the effectiveness of the solution. These experiments were carried out with the idea of finding some solution which would aid in the dissolution of calculi in the urinary tract. The one which proved the most effective, as judged by its ability to dissolve calcium phosphate and by its lack of irritating effects on the rabbit's bladder, was as follows:

Citric acid (monohydrate).....	32.3 Gm.
Magnesium oxide (anhydrous).....	3.8 Gm.
Sodium carbonate (anhydrous).....	4.4 Gm.
Distilled water to make.....	1,000 cc.

Barney⁷² discusses the paper of Suby, Suby and Albright and mentions 2 cases in which renal stones were dissolved. The first patient had a recurrent staghorn calculus in the left kidney. The kidney showed poor function, and on the opposite side there was an atrophic kidney with a double pelvis, each half of which contained

70. Flocks, R., in discussion on Jewett, Sloan and Strong.⁶⁹

71. Suby, H. I.; Suby, R. M., and Albright, F.: Properties of Organic Acid Solutions Which Determine Their Irritability to the Bladder Mucous Membrane and the Effect of Magnesium Ions in Overcoming this Irritability, *J. Urol.* **48**:549-559 (Nov.) 1942.

72. Barney, J. D., in discussion on Suby, Suby and Albright.⁷¹

a stone. The left kidney was exposed through a nephrolithotomy incision, as much of the stone removed as could be reached and a nephrostomy tube inserted. The kidney was irrigated with sodium citrate-citric acid solution, and the remaining fragments were completely dissolved. The second patient had large bilateral stones. The right kidney was exposed; the cortex was opened at the upper pole and a piece of stone removed. Into this cavity an open-ended mushroom catheter was sutured. The renal pelvis was then opened and a similar catheter sutured in place. In this way a through and through stream of the dissolving fluid was maintained. After a number of solutions had been used, levulinic acid was finally employed. No untoward reactions occurred, but its dissolving power was not as strong as that of the citric acid solution. After several weeks of irrigation, only small fragments of stone remained. Nothing was done to the stone in the opposite kidney.

Keyser⁷³ discusses the paper of Suby, Suby and Albright and states that following the lead of chemists who have determined the solubility factors of hydrogen ion concentration and magnesium, phosphate and citrate ions, numerous investigators have worked with various solutions in an effort to speed up dissolution of carbonate and phosphate stones, both in vitro and in the patient. Keyser states that as yet he has not given detailed accounts of the many efforts he has made in attempting to dissolve such calculi, with an unending variety of acids and ion combinations, but he has spoken of this frequently in generalities. One point has been emphasized, namely, that the solvent action of any solution on a dense stone is impeded by the organized matter which remains around the surface of the stone after the superficial salts are dissolved.

Keyser has studied the rate of dissolution of stones with citrate buffers, hexametaphosphate mineral acids and other solvents. The citrate mixture of Albright has been found most satisfactory, but, again, as soon as surface dissolution is effected, a gel-like envelope encompasses the stone and the dissolution process is slowed down.

Treating the calculus with ferments previous to the application of solvents was next tried, the hypothetic principle being that the enzyme might cause disintegration of the organic envelope. At least partial success in the test tube has been achieved. It was found that solutions of urease in 0.5 per cent strength applied for a brief time to calcium phosphate calculi would bring about remarkable acceleration of the dissolution, when they were irrigated in a special apparatus with Albright's citrate mixture. Thus a stone which under standard conditions of weight, composition and density would likely require twenty-four hours of irrigation to dissolve would disintegrate in one or two hours after being exposed to the urease solution for a short time. Rather paradoxically it was shown that prolonged treatment with urease solution would slow down the rate of dissolution.

Keyser has had but one clinical opportunity to apply this technic of dissolution of stones. He had two months previously removed a large stone of phosphatic composition from the left kidney of this patient, and nephrostomy had been done. She also had a right ureteral calculus, which had partly destroyed the right kidney. In addition she was the victim of a left hemiplegia. About six weeks after the operation calcific shadows of recurring calculi appeared in the left kidney. Alternate application of 0.5 per cent urease solution and irrigation with the solvent mixture of Suby and his associates through the nephrostomy tube brought about complete dissolution of this calcareous material in five days, as revealed by the roentgen rays.

73. Keyser, L. D., in discussion on Suby, Suby and Albright.⁷¹

ANURIA

Mayo and Schlicke,⁷⁴ in discussing anuria after operations on the colon and rectum, state that prophylaxis is the most effective method of dealing with this condition. Care should be exercised at the operating table to avoid undue trauma to the ureters and bladder. Routine dissection of the ureters in pelvic operations is dangerous and unsound. After operation, the output of urine must be watched carefully. The most dangerous period is after the first week. Fluids intended for parenteral administration are withdrawn, because the patient seems to be doing well, and he is left to his own resources for intake of fluids. If the intake of fluid decreases at this stage, when post-traumatic edema is at its peak, anuria may occur. Great care should be used in the administration of sulfonamide compounds, especially to older patients who already have symptoms of obstruction.

At the first sign of diminishing urinary flow—and such signs unfortunately are frequently overlooked or attributed to improper charting—prompt action is required. After simple retention of urine has been ruled out by catheterization of the bladder, the most important thing is to find the cause. Since dehydration is usually the paramount factor, this should be remedied without delay. Aqueous solutions of dextrose afford the most readily available sources of water for renal excretion, particularly if hypertonic solutions are used. Theophylline with ethylenediamine is a valuable stimulant to a sluggish kidney. Studies of blood chemistry should be carried out to determine the degree of nitrogen retention present and the extent of disturbance of acid-base equilibrium. Acidosis or alkalosis should be corrected. A plain roentgenogram of the abdomen will reveal the presence of opaque calculi. A careful physical examination should be carried out to detect the presence of associated conditions. If routine measures do not restore urinary flow, cystoscopic examination should be carried out without delay. Ureteral obstruction usually can be relieved by catheterization, but if the obstruction is bilateral and impassable, nephrostomy must be performed. A stormy course with pain suggests an obstructive type of anuria. A history of chemotherapy is important. Many of the measures often employed are of doubtful value. Sweating and purging exhaust the patient, further deplete the body of fluids and electrolytes and fail to eliminate nitrogenous waste. Heat applied to the renal regions finds its greatest usefulness in the comfort which it may afford the patient. Surgical procedures, such as splanchnic block anesthesia, decapsulation and peritoneal dialysis, often serve only to precipitate death.

PYURIA

Braasch⁷⁵ states that pus cells found in the voided urine of the female patient are of little or no clinical significance. In such instances a specimen of urine obtained by catheter is necessary. Pus cells in the voided urine of the male patient are of greater clinical value, particularly if the two glass test is employed. It is of equal clinical importance to determine the presence and kind of bacteria in the urine. Intelligent treatment of pyuria is dependent on a knowledge of its bacteriologic aspects. Rough identification of the type of organisms present is possible by the simple method of Gram's staining of the urinary sediment.

Bacillary infection is observed in most cases. Colon bacilli and *Aerobacter aerogenes* are the organisms usually found. Mixed infection may be present; most

74. Mayo, C. W., and Schlicke, C. P.: *Anuria After Operations on the Colon and Rectum*. *J. Urol.* 48:207-218 (Aug.) 1942.

75. Braasch, W. F.: *The Clinical Significance and Treatment of Pyuria*, *Ann. Int. Med.* 17:943-951 (Dec.) 1942.

often it is caused by colon bacilli with *Str. faecalis*. Unless this fact is recognized, chemotherapy may fail. Renal tuberculosis is a frequent cause of pyuria which resists chemotherapy. In recent years the symptoms and severity of the infection caused by renal tuberculosis have become milder and the recognition of such tuberculosis often is difficult.

Pyuria may be coincident with lesions situated in other organs. Acute cholecystitis coincident with pyuria often is observed. When a lesion requiring surgical attention is present, the question might arise: Would urinary infection interfere with operation? As a rule it does not, but a search should be made for the cause of the pyuria. A careful search for foci of infection and removal of them are always necessary. Pyuria or a history of previous infection of the urinary tract occurring with hypertension should be the guide to complete urologic investigation. In the presence of pyuria important clinical data can be obtained by such simple tests as the making of roentgenograms and excretory urograms.

Intelligent chemotherapy depends on identification of the bacteria. In cases in which the situation is complicated, infection caused by *Escherichia coli* often responds to treatment with mandelic acid. Of the sulfonamide compounds, sulfathiazole and sulfadiazine probably are preferable. Experience has shown that an initial daily dose of 3 or 4 Gm. is all that is necessary against most uncomplicated infections in the urinary tract. In fact, the effective dosage is gradually being reduced, and in most cases an initial dose of 3 Gm. daily for two days is being replaced by one of 2 Gm. administered for a period of six or eight days. When such a low dose is employed, the severe reactions to sulfonamide compounds described by those who employ them in treating profound systemic infections are seldom seen. Urologists have the advantage that the infected field is immersed in fluid containing the sulfonamide compound as is also the surrounding zone of reaction in the tissues, although the latter is the predominating factor. In contrast to the procedure in the treatment of systemic infection with a sulfonamide compound, it seldom is necessary to determine the concentration of the drug in the blood in treating infection of the urinary tract, since this concentration is low and does not exert much influence so far as results are concerned.

The danger of acetylation with deposition of crystals and the occurrence of anuria must be considered. Although there is a difference in the degree of acetylation caused by the various sulfonamide compounds, they all may be guilty of renal blockage. The degree of subjective toxic reaction which results is no criterion. The drug which causes the least symptomatic reaction (sulfadiazine) is one of the worst offenders in this respect. Anuria associated with the use of sulfadiazine demands the immediate cooperation of the urologist. By the introduction of ureteral catheters and lavage of the ureters and the renal pelves, the blockage usually can be relieved. It is obviously advisable to start such treatment in the early stages of anuria. Crystallization otherwise may become so dense that lavage is futile and injury to the renal cells may be fatal.

Persistent pyuria in spite of chemotherapy usually is caused by some underlying pathologic lesion in the urinary tract which requires careful examination and treatment by the urologist.

OSTEITIS PUBIS

Kleinberg⁷⁶ reports the case of a woman who had pubic osteitis due probably to the colon group of bacilli. The lesion resembles in many of its features the disease commonly seen in men as a sequel of a suprapubic prostatectomy. This case

76. Kleinberg, S.: Osteitis Pubis, with a Report of a Case in a Woman. *J. Urol.* 48:635-641 (Dec.) 1942.

makes the third one thus far described in women and for this reason is unusual, since most of the patients have been men. The temperature range was higher than in the average case, but it is difficult to say whether this was due to the pubic osteitis or to the pyelonephritis. Presumably, however, the fever was caused by the osteitis, for it subsided promptly after the pelvis was immobilized.

PRIAPISM AND SICKLE CELL ANEMIA

Getzoff⁷⁷ discusses priapism and sickle cell anemia and reports 3 cases. He states that the mechanism of occurrence of thrombosis in the vascular system of the penis in cases of sickle cell anemia still awaits final acceptable explanation. A significant feature in the pathology of sickle cell anemia is the dilated capillaries, which are engorged with the abnormal cellular forms. Numerous instances of thrombosis and infarction in cases of sickle cell anemia have been reported in the literature to testify to the potential vascular complications of this blood dyscrasia. One theory to explain the mechanism of "sickling" is that the patient possesses an inheritable alteration in the hemopoietic system. The erythrocytes, unlike normal erythrocytes, absorb an unknown substance found in plasma. Although unanimity of opinion is lacking in regard to the etiology of sickle cell anemia, it may well be that each hypothesis will have contributed an integral share to the ultimate accepted facts. These theoretic considerations of sickle cell anemia have been applied to the clinical problem of priapism in an endeavor to bridge these two important entities.

When a prolonged erection is maintained, a reduction of venous return is associated with the engorgement of the cavernous bodies. The subsequent effect of this relatively sluggish status of the vascular bed of the penis may be a lowering of the oxygen tension and a temporary local reduction in the p_H of the blood and the release of those hematologic factors which influence sickling. An unusual cohesive attraction and tendency to formation of rouleaux may occur among sickle cells in the presence of relative stasis. If such large scale cellular aggregate formations and agglutination actually take place, the modus operandi of thrombus formation is set in motion. The thrombi act to occlude some of the vascular channels concerned with the venous return from the penis; further stasis occurs. A vicious cycle comes into play, and priapism ultimately takes place.

GRANULOMA INGUINALE

Tomskey, Vickery and Getzoff⁷⁸ discuss the treatment of 102 patients with granuloma inguinale and evaluate the various modern accepted methods of treatment. The latter are contrasted with a new mode of therapy which consists of local application of 20 per cent resin of podophyllum U. S. P. in olive oil and scarlet red ointment. The prolonged hospital stay and the too frequent futile endeavors to control the progress of the lesions of granuloma inguinale with antimony and potassium tartrate alone or with these drugs and surgical procedures have proved these therapeutic methods to be relatively ineffectual as compared with the results obtained with resin of podophyllum. The therapeutic value of resin of podophyllum for granuloma inguinale is emphasized by the fact that permanent cures have been attained with this drug, a result which previously has never been obtained in Tomskey, Vickery and Getzoff's experience.

77. Getzoff, P. L.: Priapism and Sickle Cell Anemia: A Report of Three Cases, *J. Urol.* **48**:407-411 (Oct.) 1942.

78. Tomskey, G. C.; Vickery, G. W., and Getzoff, P. L.: The Successful Treatment of Granuloma Inguinale, with Special Reference to the Use of Podophyllin, *J. Urol.* **48**:401-406 (Oct.) 1942.

PATHOLOGIC STUDY OF DEGENERATION AND RUPTURE OF THE SUPRASPINATUS TENDON

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Rupture of the tendons of the short rotator cuff of the shoulder joint, notably the supraspinatus tendon, is important because of the frequency of its occurrence and because of the disability that may follow. The whole subject of rupture of the short rotator tendons of the shoulder has been reviewed at length by one of us (C. L. Wilson) in another publication.¹ The purpose of this paper is to present a gross and microscopic study of the supraspinatus tendon at various ages made especially with a view to amplifying the present rather scanty information regarding the pathologic changes in the tendon leading to rupture.

McMaster,² from experiments on rabbits, has shown that when a system composed of a muscle and its tendon, together with their bony attachments, is stretched to the breaking point by a force exerted through the bones the break occurs anywhere but in the tendon, unless the tendon has been previously injured. It will be shown in this paper that when a similar system composed of the normal supraspinatus tendon and its attachments is subjected to breaking strain, the break in this system, too, occurs at any point except in the tendon. Therefore, some lesion of the supraspinatus tendon that weakens it must be postulated to account for the occurrence of rupture as observed clinically. Such a lesion has not, hitherto, been specifically described or specifically related to rupture. Indeed, the microscopic observations on degenerative disease and rupture of the supraspinatus tendon have been relatively few and inconclusive. Codman³ described abnormalities consisting of irregularity in the staining of the fibrocartilage at the tendon insertion, loss of the smooth contour of the thin line of calcified fibrocartilage (the "blue line") at its junction with the bony cortex, changes in the thickness of the latter and what he called hyaline degeneration of the tendon bundles. Lindblom⁴ spoke of the latter change in the substance of the tendon as "homogeneous sclerosization." Both these authors expressed the belief that areas of degeneration in the tendon stained more deeply with eosin than their surroundings, a view that is quite the reverse of the

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1. Wilson, C. L.: Lesions of the Supraspinatus Tendon: Degeneration, Rupture and Calcification, *Arch. Surg.* **46**:307 (March) 1943.

2. McMaster, P. E.: Tendon and Muscle Ruptures: Clinical and Experimental Studies on the Causes and Location of Subcutaneous Ruptures, *J. Bone & Joint Surg.* **15**:705, 1933.

3. Codman, E. A.: The Shoulder: Rupture of the Supraspinatus Tendon and Other Lesions in or About the Subacromial Bursa, Boston, The Author, 1934.

4. Lindblom, K.: On Pathogenesis of Ruptures of the Tendon Aponeurosis of the Shoulder-Joint, *Acta radiol.* **20**:563, 1939; Arthrography and Roentgenography in Ruptures of Tendons of the Shoulder, *ibid.* **20**:548, 1939.

conclusion reached in the present study. However, we are able to confirm that degenerative changes are frequently to be found in the supraspinatus tendon after the age of 30 years. In the body of this paper, a degenerative lesion of the supraspinatus tendon is described in its various stages of development. This lesion is of such a character as to cause weakening of the tendon, and its occurrence shows a close correlation with the occurrence of rupture of the supraspinatus tendon. The findings are such as to justify the conclusion that the lesion described is responsible for the weakening of the tendon that leads finally to rupture.

MATERIALS AND METHODS

Both shoulders were examined in an unselected series of 90 bodies at autopsy and 35 anatomic cadavers, the total number of bodies examined thus being 125. The method of gross examination was to extend the routine autopsy incision up to the tip of the shoulder and then to free the skin from the underlying tissues. The deltoid muscle was divided transversely, with the arm in the anatomic position to insure exposure of the subacromial bursa, which was then opened. To give adequate exposure of the short rotator cuff, the coracoacromial ligament was divided. The next step was to locate and examine the tendon of the long head of the biceps muscle in the bicipital groove. If the tendon was found to be intact, a knife was passed up the groove, medial to the tendon, cutting the transhumeral ligament, the joint capsule and the few overlying blending fibers of the supraspinatus and subscapularis tendons. This incision was carried up past the musculotendinous junction of the supraspinatus muscle, across the muscle and down the other side of the tendon to its insertion on the greater tuberosity. In the autopsy series the tendon and its bony attachment were removed intact and inspected for rupture. A rupture of one or more of the tendons of the short rotator cuff was recorded as a complete rupture when it allowed free communication between the subacromial bursa and the cavity of the shoulder joint. A partial tear of the fibers that did not allow free communication between the subacromial bursa and the shoulder joint was counted as a partial rupture. The length of the intact tendon was measured, and then the specimen was preserved in Helly's or Zenker's solution for histologic examination. In the autopsy series the circumference of each arm at the level of the belly of the biceps was noted and the spinal column was inspected for scoliosis and vertebral lipping.

The specimens for histologic examination, including bone, were decalcified in an aqueous solution made up of equal parts of 50 per cent formic acid and 20 per cent sodium citrate. The histologic sections were stained routinely with hematoxylin and eosin and with Mallory's stain for connective tissue. Selected sections were stained with Weigert's and Verhoeff's stains for elastic tissue, stains for mucin, Van Gieson's stain for connective tissue and Perles' stain for iron. Since the bone contained in all of these sections had been decalcified, a control set of sections was made of tendons that had not been exposed to the action of the decalcifying solution, to determine whether decalcification had any effect on the staining properties of the tendons. When it had been established that the staining properties were unaffected by decalcification, controls were discontinued.

The tensile strength of various tendons other than the supraspinatus was determined by use of tendon clamps which were modified from Cronkite's clamp.⁵ The tensile strength of a limited number of supraspinatus tendons and muscles and their bony attachments was measured by pulling the system apart by a force applied through steel pins inserted in the bones. In these experiments a Tinius Olsen Universal Tension Machine, accurate to 0.5 per cent, was used.

OBSERVATIONS

Incidence of Rupture.—Since rupture of the supraspinatus tendon has never been reported in a patient less than 32 years of age,¹ only subjects over 30 years of age were used in assessing the frequency of rupture. This excluded 16 bodies from the autopsy series and 1 from the cadaver group. In the autopsy series complete rupture occurred in 15 of 74 bodies over 30 years of age, that is, an incidence of 20 per cent. There were 8 unilateral ruptures and 7 bilateral.

In the cadaver group complete rupture occurred in 9 of 34 bodies, an incidence of 26.5 per cent. Four ruptures were unilateral, and 5 were bilateral.

⁵ Cronkite, A. E.: Tensile Strength of Human Tendons, *Anat. Rec.* 64:173, 1936.

The average age of all autopsy subjects over 30 was 55 years and of cadaver subjects 66 years. In spite of this, the average age of subjects with complete rupture was virtually the same in the two groups. In both groups taken together, the average age of the subjects with complete rupture was 65 years and the incidence was 22.2 per cent of the bodies examined. The youngest subject with complete rupture was a man 48 years of age, and the oldest was a woman 87 years of age. The incidence among men was 23.7 per cent and among women was 17.8 per cent.

In the autopsy series unilateral complete rupture occurred on the right side six times and on the left side twice. In every instance of unilateral complete rupture the circumference of the arm at the level of the belly of the biceps was at least 1 cm. greater on the side of the rupture than on the opposite side. In the cadaver series, in which no measurements of arm circumference were made, the unilateral complete ruptures all occurred on the right side. It should also be noted that in both series whenever a bilateral rupture occurred the defect in the rotator cuff was always larger on the right side.

Partial rupture of the supraspinatus tendon observed in the autopsy series occurred in 15 subjects of 74 over 30 years of age, an incidence of 20 per cent. Eight of the ruptures were unilateral, three were bilateral and four were unilateral but were associated with a complete rupture of the supraspinatus tendon of the opposite side. Of the eight unilateral partial ruptures, six occurred on the right side and two on the left side. In all but 1 of the bodies the rupture was on the side of which the arm had the greater circumference when measured around the belly of the biceps. Not much difference was noted in the size of the partial ruptures between the two sides when the rupture was bilateral. Of the four partial ruptures associated with a complete rupture of the opposite supraspinatus tendon, two occurred on the right and two on the left. The partial ruptures were all on the side of the smaller arm, and the complete ruptures were on the side of the larger arm. The average age incidence of partial rupture of the supraspinatus tendon was 62 years.

In 8 persons out of the 108 over 30 years of age, there was rupture of the long head of the biceps tendon as well as complete or partial rupture of the supraspinatus tendon, an incidence of 7.4 per cent. Four of the subjects had bilateral rupture and four unilateral (12 ruptures in all).

Gross Observations.—As one would expect, the supraspinatus tendon is longer in an adult than in a child. Measurements of the tendon in subjects of different ages showed, however, that once adult age was reached the normal tendon did not increase in length with increasing age. It should be emphasized that since the muscle inserts into the tendon in semicircular fashion it is necessary to measure the tendon after it has been split through the middle in order to obtain consistent measurements. It is also important to note that abnormality of the tendon short of complete rupture can cause measurable lengthening. In 23 adult subjects of different ages, the supraspinatus tendons on superficial examination appeared normal but the measurements showed that the right tendons averaged 0.4 cm. longer than the left. It was then discovered on more careful examination that a number of the tendons from the right side were not really normal. These showed a partial rupture involving the joint capsule and adjacent fibers of the tendon, which had lost their attachment to the sulcus and the greater tuberosity of the humerus. This type of lesion, known as a rim rent, causes a decrease in the thickness of the tendon at its insertion and a definite increase in its total length. When this source of error was corrected by omitting persons with rim rent, it was found in a series of 40 subjects with normal supraspinatus tendons that the

tendons were of equal length on the two sides, averaging 2.25 cm. on each side. Only 2 of these subjects were left handed, as judged by a larger circumference of the left arm measured at the level of the belly of the biceps muscle.

The gross pathologic changes in rupture of the supraspinatus tendon have been described adequately in the literature.⁶ The observations in the present study, confirming those of previous investigators, were briefly as follows: Partial ruptures were characterized by the presence of a tear near the insertion of the tendon but involving only a part of its thickness and not forming an open rent that would allow communication between the joint cavity and the subacromial bursa. Such incomplete ruptures in some instances involved the fibers nearest the joint cavity (rim rent) and in others the tendon layer just beneath the subacromial bursa; in still others they involved the central part of the thickness of the tendon without affecting either surface. In the complete ruptures there was a tear across the



Fig. 1.—Photograph of dissection of the right shoulder joint. The tendons of insertion of the supraspinatus, infraspinatus and teres minor muscles and the capsule of the shoulder joint have torn away, the head of the humerus thus being allowed to come into direct contact with the under surface of the deltoid muscle. There are extensive erosion of the head of the humerus and recession of the greater tuberosity. The intra-articular portion of the tendon of the long head of the biceps muscle has been lost, while the lower portion (indicated by the scalpel passed beneath it) has become attached at its upper end to the bicipital groove.

6. (a) Davis, T. W., and Sullivan, J. E.: Rupture of the Supraspinatus Tendon, *Ann. Surg.* **106**:1058, 1937. (b) Horwitz, M. T.: Lesions of the Supraspinatus Tendon and Associated Structures: Investigation of Comparable Lesions in Hip-Joint, *Arch. Surg.* **38**: 990 (June) 1939. (c) Keyes, E. L.: Observations on Rupture of Supraspinatus Tendon Based on Study of Seventy-Three Cadavers, *Ann. Surg.* **97**:849, 1933; Cadaver Observations: Anatomical Observations on Senile Changes in the Shoulder, *J. Bone & Joint Surg.* **17**:953, 1935. (d) Meyer, A. W.: Further Evidences of Attrition in the Human Body, *Am. J. Anat.* **34**: 241, 1925-1926; Unrecognized Occupational Destruction of the Tendon of the Long Head

(Footnote continued on next page)

supraspinatus tendon near its insertion, sometimes extending to involve the tendons of the infraspinatus, teres minor or subscapularis muscles. The defects thus produced allowed free communication between the cavity of the shoulder joint and the subacromial bursa. Complete ruptures of some duration showed retraction, thickening and rounding of the torn edges with the formation of a triangular defect, the base of which was on the greater tuberosity of the humerus. If the rupture was recent the latter bore the stub of the ruptured tendon, but if the rupture was of longer standing the torn end of the tendon attached to the greater tuberosity was scarcely discernible, or had disappeared altogether (fig. 1).

In cases of rim rent or of complete rupture of the supraspinatus tendon, associated changes of varying degree in the articular cartilage of the head of the



Fig. 2.—Photomicrograph of a histologic section of normal supraspinatus tendon, showing the typical arrangement of the wavy collagen bundles and the thin elongated nuclei of fibrous connective tissue cells. Note the absence of visible blood vessels. Hematoxylin and cosin; $\times 98$.

humerus were frequently seen. These consisted of slight roughening, fraying or erosion of the cartilage in a position corresponding with that of the defect in the supraspinatus tendon but involving an area somewhat larger than that of the defect in the tendon. Moreover, there appeared to be a relation between the

of the Biceps Brachii, Arch. Surg. 2:130 (Jan.) 1921; Chronic Functional Lesions of the Shoulder, *ibid.* 35:646 (Oct.) 1937. (e) Skinner, H. A.: Anatomical Considerations Relative to Rupture of the Supraspinatus Tendon, J. Bone & Joint Surg. 19:137, 1937. (f) Wilson, P. D.: Complete Rupture of the Supraspinatus Tendon, J. A. M. A. 96:433 (Feb. 7) 1931; The Painful Shoulder, Brit. M. J. 2:1261, 1939. (g) Codman³

occurrence of pronounced changes in the articular cartilage and rupture of the tendon of the long head of the biceps muscle. In all cases of rupture of the biceps tendon there was definite erosion of the cartilage of the head of the humerus, over which the intracapsular portion of the biceps tendon had run. In 10 instances there was a complete rent in the supraspinatus tendon through which the roughened and eroded head of the humerus could be seen when the subacromial bursa was opened. In the other 2 instances there was only a rim rent of the supraspinatus tendon and less erosion of the head of the humerus. In 10 of the instances of rupture of the biceps tendon, the upper end of the lower portion of the tendon was fused to the bicipital groove (fig. 1), and in 2 of these there was also an attachment to the transhumeral ligament, the biceps tendon being apparently split

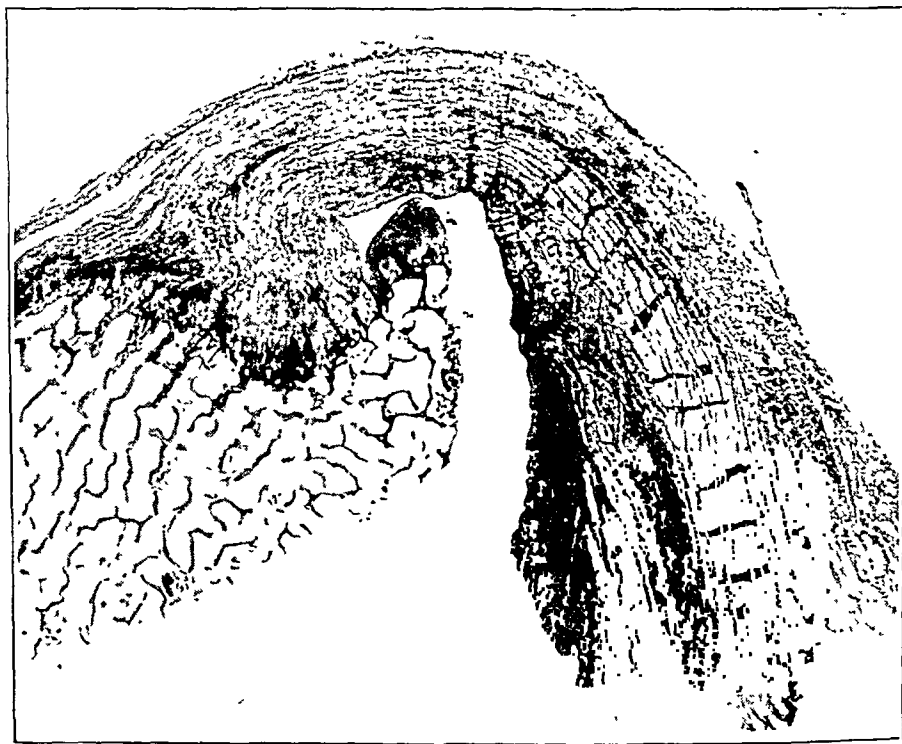


Fig. 3.—Photomicrograph of a histologic section of normal supraspinatus tendon and its insertion. The dark borders on the upper and lower surfaces of the tendon aponeurosis represent the base of the subacromial bursa and the capsule of the shoulder joint, respectively. Only the pale central portion is true tendon. Mallory's stain for connective tissue; $\times 4.2$.

in two. In these 10 instances of rupture, there was no discernible remnant of the biceps tendon above the transhumeral ligament. In 2 instances the biceps tendon showed no attachment to the bicipital groove but the intracapsular portion was fused to the under surface of the joint capsule, leaving no free portion within the joint. The glenoid attachment of the tendon was discernible as a bandlike structure.

Microscopic Observations.—Microscopic study of the supraspinatus tendon in subjects of different ages showed that the tendon bundles increase in diameter and presumably in length from infancy to adult life. In all normal tendons the

wavy appearance of discrete collagen bundles was readily seen but the fibroblasts lying between the bundles were represented only by elongated dark nuclei lying parallel with the collagen fibers (fig. 2). It should be noted that the tendon forms only part of the depth of the tissue composing the musculotendinous cuff. The rest is made up of the base of the normally thin subacromial bursa above and the capsule of the shoulder joint below. Codman's sketch³ does not show this point, but it is brought out clearly with Mallory's stain for connective tissue, which colors the base of the bursa and the joint capsule blue and the tendon orange (fig. 3). The number of arterioles has been found by many to decrease with

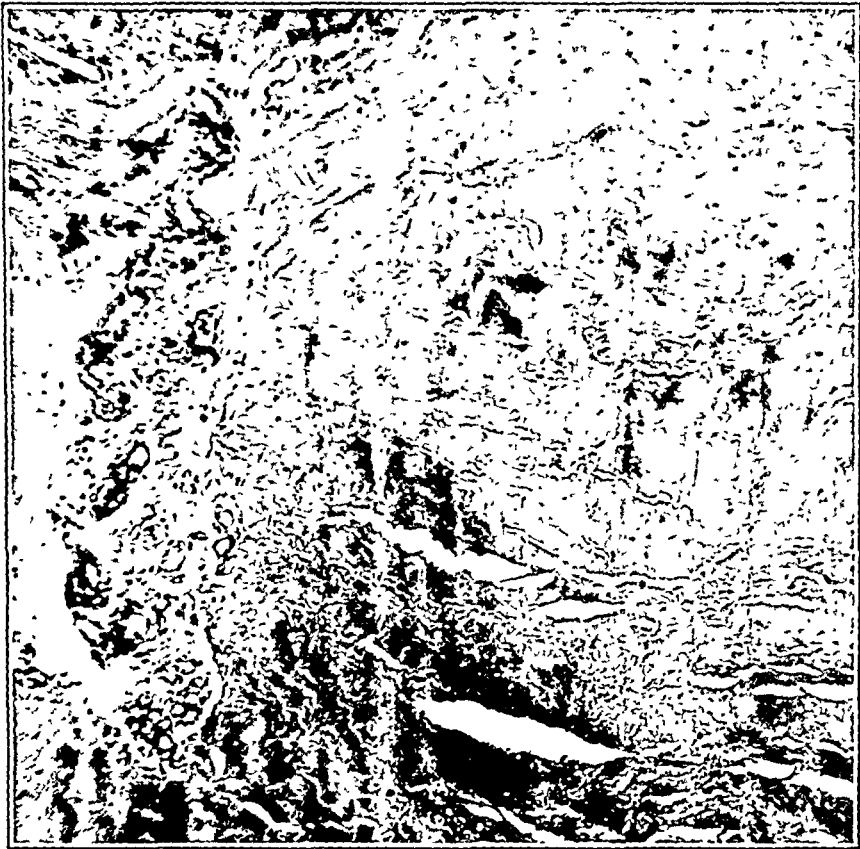


Fig. 4.—Photomicrograph of a histologic section of supraspinatus tendon near its insertion, showing loss of normal wavy outline of tendon bundles, with fusion into a homogeneous mass, in which the nuclei of connective tissue cells are distorted, rounded or pyknotic. There is a downgrowth from the floor of the subacromial bursa of loose fibrous tissue containing many thick-walled blood vessels. Hematoxylin and eosin; $\times 110$.

age.⁷ This was confirmed in the present study. Numerous arterioles were seen in the supraspinatus tendon in infancy and childhood, but the number gradually decreased up to 40 years of age. After the age of 40 years, arterioles were seen relatively rarely in normal tendons.

7. Rau, cited by Honigsman, F.: *Med. Klin.* **22**:728, 1926. Sobotta, J.: *Atlas of Human Histology and Microscopic Anatomy*, translated by W. H. Piersol, New York, G. E. Stechert & Company, 1930. McMaster.²

Special stains were used to study the component parts of the supraspinatus tendon. No elastic tissue could be demonstrated in the tendons or at most only a few very fine fibrils. Stains for mucin and for iron produced negative results in both normal and degenerate tendons. Decalcification in formic acid-sodium citrate solution did not affect the staining reactions of tendons to hematoxylin and eosin or to Mallory's stain for connective tissue. A normal tendon stains a deep pink with eosin and orange with Mallory's stain. The structure of the supraspinatus tendon just before it inserts into the bone is that of fibrocartilage, and where it joins the bony cortex a narrow band becomes calcified and forms a blue line when stained with hematoxylin.

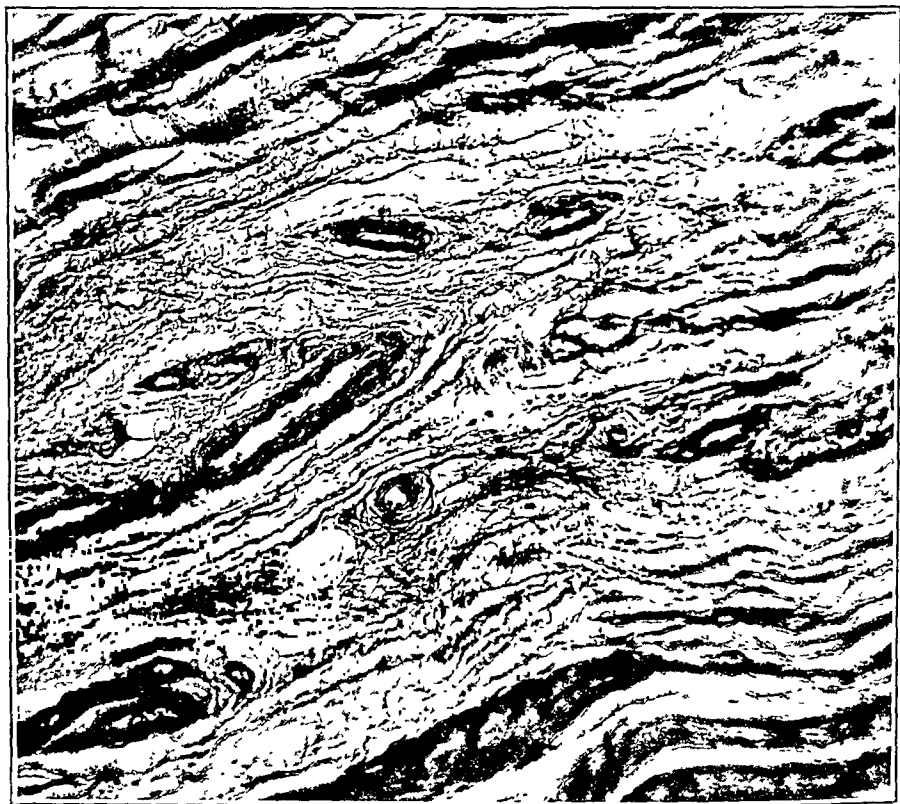


Fig. 5.—Photomicrograph of a histologic section of supraspinatus tendon near its insertion, showing a more advanced stage of degeneration. The fibrillar tendon structure has a loose edematous appearance. Note the numerous thick-walled arterioles. Hematoxylin and eosin; $\times 104$.

In many of the subjects with intact supraspinatus tendons, certain degenerative changes in these tendons were observed on microscopic examination. These changes tended to be greater in degree with advancing years. They were more prominent than would be expected on the basis of age alone in those who, to judge by their clinical history, had done heavy manual labor. Changes of the same kind were found in still more pronounced degree in partially ruptured supraspinatus tendons, and the most severe alterations were seen in tendons which had ruptured completely. It seemed evident that the observed abnormalities bore some relation to the spontaneous occurrence of partial or complete rupture of the supraspinatus tendon.

The degenerative changes referred to in the supraspinatus tendon were characterized by alterations in the tendon itself and also in its insertion. The earliest histologic evidence of abnormality in the structure of the tendon in sections stained with hematoxylin and eosin was a granularity and loss of the normal clear wavy outline of individual collagen fibers and bundles of such fibers. They became straighter and tended to merge with one another so that individual fibers and bundles were obscured and the whole structure took on a rather homogeneous appearance (fig. 4). Such homogeneous strands in the tendon stained less deeply with eosin than the normal portions. The arrangement of the nuclei of connective tissue cells became somewhat disordered; they lay with their long axes in various directions, not necessarily parallel with the direction of the collagen fibers. Moreover, the nuclei had a shrunken, distorted appearance; some of them were rounded, vesicular and rather faintly stained with hematoxylin while others were pyknotic (fig. 4). With the further development of these changes, the homogeneous areas in the tendon took on a somewhat gelatinous or edematous appearance, with a loosening of the constituent fibers, which again became visible. However, these fibers no longer had the plump, smooth appearance of normal collagen but consisted of a sparse and broken network of frayed and shredded threads widely separated by a pale-staining homogeneous material that suggested a fluid or semifluid consistency (fig. 5). The homogeneous interfibrillar material did not give the staining reactions of mucin. The fibrillar appearance of the tendon structure at this stage must be differentiated from a somewhat similar appearance that may be produced as an artefact in cutting sections from blocks of tissue in which the bone has been insufficiently decalcified.

In histologic sections stained with Mallory's stain for connective tissue, progressive changes in staining properties ran parallel with the alterations just described. The collagen bundles of the normal tendon stain a brilliant orange with this stain, the color being uniformly and smoothly spread along the fibers. In degenerating tendons, however, the orange staining first became irregular. Small patches in the bundles of collagen fibers showed no orange staining or were only lightly stained, while in neighboring areas there appeared little accumulations or "pools" of a homogeneous material resembling a thick fluid which stained deeply orange. The loss of the staining properties of tendon bundles progressed in patchy fashion until only a few small areas showed any staining with orange and the remainder stained blue instead. The little "pools" of orange-staining material did not become large but remained visible in degenerated areas bordering on those parts of the tendon in which more or less normal staining still prevailed. This progressive loss of the orange-staining property corresponded with alterations in the tendon leading to the homogeneous appearance already described as seen in sections stained with hematoxylin and eosin. In tendons that had passed beyond the "homogeneous" stage and showed fibrillation, the greater part of the tendon stained blue with Mallory's stain and only small scattered areas were tinged with orange. The whole degenerative process as observed in sections stained with Mallory's stain suggested that the normal orange-staining property of the tendon depended on impregnation of the fibers by some viscid substance which was progressively lost as the process became more advanced. This suggestion is supported by the fact that normal tendons treated by immersion in a normal solution of sodium hydroxide for one to twelve hours at room temperature stained uniformly blue with Mallory's stain and showed a complete loss of the normal orange staining, as though the substance responsible for this characteristic staining property had been dissolved out of the tendon.

As the degenerative changes just described became more advanced, there was an evident increase in the number of blood vessels in the degenerating areas. Small arterioles apparently connected with those of the subacromial bursa and the joint capsule invaded the degenerating areas accompanied by a small amount of loose connective tissue (figs. 4 and 5). Such an invasion of blood vessels into the substance of the tendon was never observed in persons over 40 years of age except in association with degenerative changes in the tendon of the character already described.

Alterations in the supraspinatus tendon were not infrequently accompanied by changes at its insertion. The fibrocartilage was in some instances rendered homogeneous and in others fibrillar, in either case staining very lightly with eosin. Abnormalities in the bony cortex of the greater tuberosity consisted of thinning or thickening or irregularity of this layer (fig. 6) with or without actual perfora-

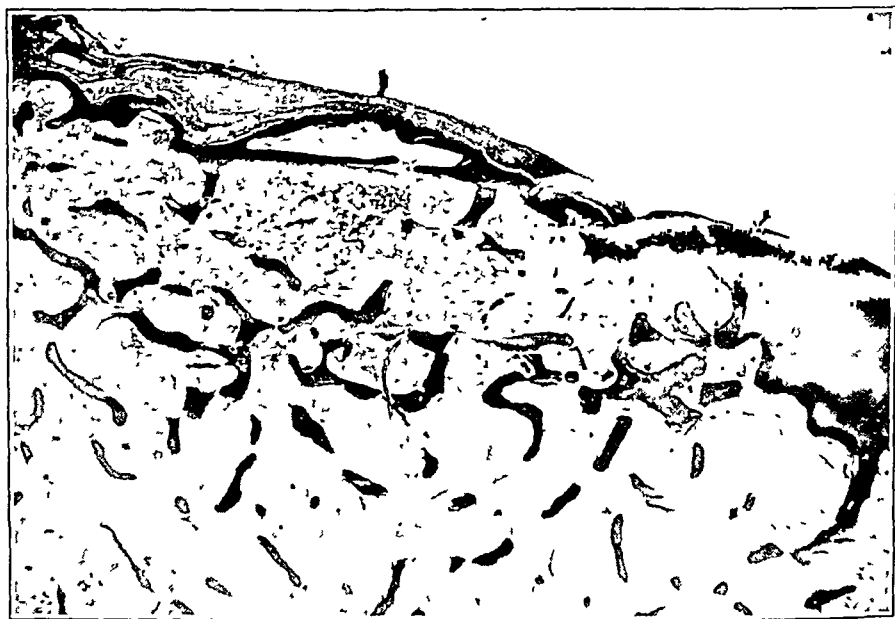


Fig. 6.—Photomicrograph of a histologic section of the greater tuberosity of the humerus, showing recession following complete rupture of the supraspinatus tendon. At the site of insertion of the tendon there is no remnant of tendon or fibrocartilage but only a thin layer of loose connective tissue covering the abnormally thin bony cortex. The margin of the articular cartilage is seen at the right side of the photograph. Hematoxylin and eosin; $\times 21$.

tion of the cortex by loose connective tissue containing many thick-walled blood vessels and giant cells.

An attempt was made to grade the degree of degeneration on a four point scale by scoring one point for each of the following features: (1) alterations in the structure of the tendon; (2) distinct changes in staining qualities; (3) increase in the number of arterioles, and (4) abnormalities at the tendon insertion. A grade of 0 represented a normal tendon, while a grade of IV represented the maximum degree of degeneration. The latter was encountered almost exclusively in ruptured tendons. Eighty-four supraspinatus tendons from the right side and 85 from the left side were graded on this basis, and the results are set out in the table, which serves to show clearly the relation of age to the degree of severity of degenerative changes in the supraspinatus tendon.

In a limited number of cases the tendon of the long head of the biceps muscle was examined microscopically. Its normal structure was found to be the same as that of the supraspinatus tendon. Degenerative changes were also observed. These were of the same kind and were characterized by the same features as already described in the supraspinatus tendon. The degree of degenerative change in the tendon of the long head of the biceps was generally comparable to that of the supraspinatus tendon of the same shoulder.

Tensile Strength.—By tests on tendons taken from various locations in the body, it was found that a tendon about 0.5 cm. in diameter would withstand a tension of over 200 pounds (90 Kg.) when the ends of the tendons, secured in special clamps, were gradually and evenly pulled apart in the tension machine. In tests of the strength of the system composed of the head of the humerus, the supraspinatus tendon and muscle and the scapula, the tension was applied slowly through pins inserted in the bones. It was found that a break generally occurred at a tension of a little less than 175 pounds (80 Kg.) and that the break occurred anywhere but in the tendon. Microscopic examination of the tendons from the specimens that had been broken in this way revealed normal or only slightly abnormal structure.

Age Distribution of Degenerative Changes in Supraspinatus Tendon

	Grade of Degeneration				
	0	I	II	III	IV
Right Supraspinatus Tendon:					
Average age of patients in each grade in years....	32.4	47.5	60.3	60.2	63.4
Number of tendons in each grade.....	27	16	14	18	9
Percentage of tendons in each grade.....	32.1	19.1	16.7	21.4	10.7
Left Supraspinatus Tendon:					
Average age of patients in each grade in years....	33.3	51.1	58.0	58.3	71.0
Number of tendons in each grade.....	28	21	17	11	8
Percentage of tendons in each grade.....	33	24.7	20	12.0	8

COMMENT

Skinner^{6c} has stated that the increased length of the tendon which occurs with age is at the expense of the muscle at the musculotendinous junction. As has been shown in the present study, a rim rent gives an apparent increase in the length of the supraspinatus tendon, but obviously a rim rent can be disregarded as one of the factors causing normal increase in the length of the tendon. In the tendons of children and adolescents there were no signs of replacement of muscle by tendon at the musculotendinous junction. That is to say, there were no intermediate stages to support Skinner's theory of muscle replacement. The fact that the average length of the supraspinatus tendons on the right and on the left side was the same would throw further doubt on Skinner's idea, since, according to his theory, use of the arm causes muscle to be replaced by tendinous tissue; if this were true, the tendon on the right in a right-handed person would be longer than the one on the left, which it is not except when a rim rent is present. It is therefore entirely reasonable to assume that the increase in width and presumably also in length of the collagen bundles of the tendon which occurs between infancy and adult age, and which can be easily seen microscopically, is enough to account for the length of an adult supraspinatus tendon.

The figures recorded in the literature on the incidence of complete rupture of the supraspinatus tendon are rather misleading, because they have usually been

based on the number of shoulders examined. A much more accurate concept is obtained if the incidence is based on the number of bodies examined, because then a case is still only 1 case whether rupture is unilateral or bilateral. The lesion is common in the older age groups, and the older the group the more frequently the lesion occurs. This is borne out in the present study by comparison of the incidence, of 20 per cent, in the autopsy series, in which the average age of the group was 55 years, and the considerably higher incidence, of 26.5 per cent, in the series of anatomic cadavers, in which the average age of the group was 11 years greater. It is worthy of note, however, that regardless of the different average ages of the two groups from which the material was drawn, the average ages of the subjects with rupture in the two groups were virtually the same, namely 65 years. This age incidence is in accord with that reported by previous investigators.¹

In the autopsy material, the circumference of the arm at the level of the belly of the biceps was taken as an indication of handedness, or at least as an indication of the relative degrees of muscular work which had been demanded of the arms during life. The arm with the larger circumference, excluding edema, was considered to be the arm that had been put to greater muscular use. This was checked by the direction of scoliosis if present, with complete agreement in all instances. In the 8 cases of unilateral complete rupture (6 ruptures on the right side and 2 on the left), the results were always consistent with the idea that a unilateral complete rupture occurs on the side that has been called on for greater muscular effort. In all cases of bilateral complete rupture the right arm was larger and more muscular than the left, as judged by the measurements of circumference, and in all the size of the rupture was much larger on the right side than on the left. The 8 unilateral partial ruptures, with 1 exception, occurred on the side of the larger arm. In the 4 cases of partial rupture associated with complete rupture of the opposite side, the partial rupture was always on the side of the smaller arm and the complete rupture on the side of the larger arm. These observations point inevitably to the conclusion that physical use of the arm is an important factor in the causation of rupture of the supraspinatus tendon, with or without associated rupture of the other rotator tendons of the shoulder joint.

It would seem that rupture of the supraspinatus tendon, either complete or partial, in the form of a rim rent, and subsequent erosion of the articular cartilage of the head of the humerus were in some way responsible for a large percentage of the ruptures of the tendon of the long head of the biceps. From the various pictures described of rupture of the long head of the biceps tendon, it is probable that the sequence of events is as follows: First there is degeneration of the supraspinatus tendon, followed by rupture, either complete or partial. Then the articular cartilage of the head of the humerus is eroded by friction against the under surface of the acromion or the coracoacromial ligament in case of complete rupture of the supraspinatus tendon or against the roughened fibers of the supraspinatus tendon in case of a rim rent. The tendon of the long head of the biceps becomes swollen and later frayed as it passes over the roughened head of the humerus. At this stage it shows microscopically the same degenerative changes as those described in the degenerate supraspinatus tendon. The long head of the biceps tendon then becomes attached to the joint capsule, with which in time it is indistinguishably blended throughout its entire intracapsular course. At the same time the roughened biceps tendon becomes attached to the humerus at the top of the bicipital groove. The end result is attachment to the bicipital groove and complete loss of the intracapsular portion.

McMaster's experiments on rabbits² and the experiments on tensile strength of the human supraspinatus tendon carried out in the present study show clearly that the normal tendon is, if not the strongest link, at least never the weakest in the bone-muscle-tendon-bone system. The normal human supraspinatus tendon will withstand a tension approaching 175 pounds (80 Kg.) without the occurrence of rupture. Indeed, the break occurs anywhere but in the tendon. In view of these facts, the clinical occurrence of rupture of the supraspinatus tendon makes it perfectly clear that prior changes must have occurred in order to permit rupture of the tendon rather than of some other part of the system. It is obvious, too, that these prior changes must be of such a character as to cause weakening of the tendon. The degenerative changes in the supraspinatus tendon described in this paper answer these requirements fully. These degenerative changes are seen more frequently and in increasing severity with increasing age, reaching a peak in the seventh decade, in which rupture most frequently occurs. They are more pronounced in men than in women and occur especially in persons who have been engaged in heavy manual work. The most advanced degenerative changes are seen in partially or completely ruptured tendons. Apart from this close correlation with the incidence of clinical rupture, the degenerative alterations observed microscopically are of a kind that would lead to weakening of the tensile strength of the tendon. It has already been pointed out that the microscopic appearances, particularly in sections stained with Mallory's stain for connective tissue, suggest a loss of some sort of binding substance from among the tendon fibers. On all of these grounds, it appears reasonable to believe that the microscopic alterations of degenerative character described in this paper constitute the cause of weakening which permits rupture of the supraspinatus tendon when a sudden, perhaps slight strain is applied.

From the data provided by this study, it is evident that age and mechanical use of the shoulder joint are important factors in causing the degeneration of the supraspinatus tendon that leads to rupture. Both the degenerative changes in the tendon and the incidence of rupture increase with advancing years, and both occur with unexpected frequency in persons who can be supposed to have done heavy manual labor. Moreover, degenerative changes are more advanced in the supraspinatus tendon of the shoulder on the more muscular side, and ruptures are more frequent on the more muscular side, both of which observations support the view that use as well as age is important in the causation of degeneration of the tendon.

While these points are clear, it is not so obvious how age and use are effective in bringing about the observed alterations in the supraspinatus tendon leading to rupture. Whether mechanical compression or attrition is able to produce the changes described in the tendon is unknown. The possible role of ischemia in this connection is difficult to evaluate. It appears that the vascularity of the supraspinatus tendon normally decreases with age in a progressive fashion, so that after the age of 40 arterioles are seldom seen in normal tendons. It might be supposed that this decrease of blood supply left the tendon with insufficient nutrition. On the other hand, however, it is found that degenerating tendons possess considerable numbers of arterioles, which are especially numerous in the most degenerated areas, definitely more numerous than normal. This might be regarded either as a "compensatory" ingrowth of new vessels to supply a part possessing insufficient circulation or as an attempt at repair of a pathologic lesion by the ingrowth of vascular connective tissue. The latter view seems much more probable. The influence of age as such is extremely difficult to separate from the influence of use, but age may be accompanied by a deterioration of the fibers composing the tendon through the

occurrence of alteration in the colloidal state of their constituents. Other factors as yet unknown may prove to be even more directly concerned than any of those mentioned, and for the time being one can state only that the pathogenesis of degeneration of the tendon is a problem of which practically nothing is known although the importance of at least two etiologic factors, age and use, seems to be clearly established.

It appears highly probable that the degenerative lesions described in the supraspinatus tendon are not by any means peculiar to that tendon. Similar changes were observed in the tendon of the long head of the biceps muscle. Indeed, it seems reasonable to suppose that changes of the same order and of similar origin may occur in various other tendinous structures in other parts of the body. Some indication that this may be so is furnished by a comparison of data regarding rupture of the supraspinatus tendon with equivalent data given by Donohue⁸ concerning rupture of the annulus lamellosus of the intervertebral disk, which permits extrusion of the nucleus pulposus. Both occur in patients over 30 years of age, and the incidence of both increases with the age of the group examined. The incidence of the two lesions is about 15 to 20 per cent of the number of bodies in which it is looked for. Both lesions are more common in men. With both, degeneration of the tendon precedes and is the cause of rupture. With both, the clinical history is that of a minor incidental trauma precipitating the rupture and causing the onset of acute symptoms. The analogy is so striking that it seems probable that these two lesions represent the result of the same process of degeneration of a tendon proceeding in different parts of the body.

SUMMARY AND CONCLUSIONS

Gross and microscopic studies were made of the short rotator tendons of the shoulder joint with special reference to the supraspinatus tendon. These tendons, together with the tendon of the long head of the biceps muscle, were examined in both shoulders in an unselected series of 125 bodies.

The average lengths of the supraspinatus tendons on the right and left sides were the same. Normal growth accounts for the increase in the length of the supraspinatus tendon which is observed from infancy to adult age. A tear of the innermost fibers of the supraspinatus tendon which includes the joint capsule (rim rent) gives an apparent increase in the length of the tendon and occurs most often and is most severe, if bilateral, on the side which has had greater use, that is, the right side.

The frequency of rupture of the supraspinatus tendon increases with the age of the group examined. The incidence of complete rupture among 108 unselected bodies over the age of 30 years was 22.2 per cent. The average age of subjects with complete rupture was 65 years. The incidence of partial rupture among 74 unselected bodies over the age of 30 years was 20 per cent, and the average age of subjects with partial rupture was 62 years.

Complete rupture of the supraspinatus tendon occurs first on the side which has been called on for greater muscular use, and in the case of bilateral rupture it is larger on that side. Therefore the majority of unilateral ruptures are on the right side, and in the case of a bilateral rupture the larger defect is on the right side.

Rupture of the tendon of the long head of the biceps muscle occurred in 7.4 per cent of the bodies examined. It was always associated with complete or partial rupture of the supraspinatus tendon and erosion of the articular cartilage of the head of the humerus. Complete or partial rupture of the supraspinatus

8. Donohue, W. L.: Pathology of the Intervertebral Disc, *Am. J. M. Sc.* 198:419, 1939.

tendon is much the most frequent, if not the only, cause of rupture of the tendon of the long head of the biceps other than severance of the tendon by a penetrating wound. After rupture of the supraspinatus tendon, the upper end of the tendon of the long head of the biceps muscle fuses with the capsule of the shoulder joint and is gradually obliterated, while the lower end becomes attached to the bicipital groove.

Weakening of the supraspinatus tendon is a necessary antecedent to rupture. When a strain is applied through the bones to a specimen consisting of scapula, supraspinatus muscle, tendon and humerus, a normal supraspinatus tendon does not rupture. Rupture occurs instead in any other part of the system.

A degenerative lesion of the supraspinatus tendon is described which is characterized by alterations in tendon structure, changes in the staining qualities and increase in the number of arterioles as well as by alterations at the insertion of the tendon. These alterations need not all be present in a given tendon, but they increase with age and may all be present in high degree. They are especially conspicuous in ruptured tendons. It is concluded that this degenerative lesion is the cause of the weakening which permits rupture of the supraspinatus tendon. Similar degenerative changes are found in the tendon of the long head of the biceps muscle.

It is pointed out that the degenerative process described as occurring in the supraspinatus tendon and the tendon of the long head of the biceps muscle probably occurs in varying degrees in other similar structures in other parts of the body. This suggestion is supported by comparison of the known data concerning degeneration and rupture of the supraspinatus tendon with the equivalent data regarding rupture of the tendinous ring of the intervertebral disk.

Prof. C. P. Martin, Department of Anatomy, McGill University, gave us permission to examine the shoulder joints in the series of anatomic cadavers referred to in this paper, and Dean Brown, of the Faculty of Engineering, placed at our disposal the apparatus used for measuring the tensile strength of the tendons.

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ANATOMIC AND CLINICAL STUDY OF THE TRANSVERSE ABDOMINAL INCISION

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The transverse abdominal incision has been used nearly one hundred years. Baudelocque¹ used it prior to 1847 for cesarean sections, but it was Pfannenstiel,² in 1900, who popularized its use in pelvic operations. Maylard³ (1899), of Glasgow, first used a transverse incision in the upper part of the abdomen. In making this incision, he sectioned all layers of the abdominal wall in a transverse plane. An intra-abdominal hemorrhage that occurred after the closure of a median vertical incision led him to employ a transverse incision for the second laparotomy. He subsequently observed that the transverse section healed more quickly and more firmly than the median vertical one, in which a hernia developed.

Boeckmann,⁴ of St. Paul, unaware of Maylard's observations, first employed the transverse incision in all types of abdominal operations in 1906. Sprengel⁵ introduced it to the Continental surgeons in 1910 and, in conjunction with Bakes, pointed out many of its advantages.⁵ Since 1910 advocates of the transverse abdominal incision have been fairly numerous. Moschcowitz⁶ (1916), Quain⁷ (1917), Moore⁸ (1922), Sloan⁹ (1927) and Bartlett and Bartlett¹⁰ (1933) have been especially interested in the problem. At the present time the transverse incision is being used by many surgeons; however, its acceptance as the abdominal incision of election is not as widespread as it should be.

As opinions on vertical and transverse incisions vary among authors, and in view of the apparent increase in popularity of the transverse variety, it was felt that an investigation of it would be timely. It was noted early that opinions and descriptions on the anatomy of the abdominal wall varied and that descriptions in standard texts were at variance with more recent work.¹¹ Careful anatomic dissections of the anterior abdominal wall were then carried out. To evaluate the clinical aspects of the transverse incision a series of 225 consecutive transverse incisions in the upper part of the abdomen were studied and compared with a similar series of 346 vertical incisions recently reported from the same hospital

From the Department of Surgery, University of Michigan.

1. Baudelocque, C. A.: *Nouveau procédé pour pratiquer l'opération césarienne*, Thesis. Paris, no. 132, 1823.

2. Pfannenstiel, J.: *Ueber die Vortheile des suprasymphysären Fascienquerschnitts für die gynäkologischen Koeliotomien*, Samml. klin. Vortr., 1900, no. 268 (Gynäk. no. 97), p. 1735.

3. Maylard, A. E.: *Brit. M. J.* **2**:895, 1907.

4. Boeckmann, E.: *St. Paul M. J.* **12**:255, 1910.

5. (a) Sprengel, O.: *Arch. f. klin. Chir.* **92**:536, 1910. (b) Bakes, J.: *ibid.* **96**:205, 1911.

6. Moschcowitz, A. V.: *Ann. Surg.* **64**:268, 1916.

7. Quain, E. P.: *Tr. West. S. A.*, 1917, p. 353.

8. Moore, W. J.: *Ann. Surg.* **75**:70, 1922.

9. Sloan, G. A.: *Surg., Gynec. & Obst.* **45**:678, 1927.

10. Bartlett, W., and Bartlett, W., Jr.: *Surg., Gynec. & Obst.* **57**:93, 1933.

11. (a) Davies, F., and Wakeley, C. P. G.: *Australian & New Zealand J. Surg.* **2**:381, 1933. (b) Davies, F.; Gladstone, R. J., and Stibbe, E. P.: *J. Anat.* **66**:323, 1932. (c) McVay, C. B., and Anson, B. J.: *Anat. Rec.* **77**:213, 1940.

by Haight and Ransom.¹² Though the two series of operations do not represent exactly alternate cases, they nevertheless are from the same general period and in most instances were performed by the same surgeons.

ANATOMY

1. *Skin*.—Langer's lines of cleavage cross the skin of the anterior abdominal wall in a generally transverse direction. An incision paralleling these lines causes the least structural and cosmetic damage to the skin. It is recognized that the residual scarring of transverse incisions is less. Evidently, the low tension on the healing transverse incision is largely responsible for the difference.

2. *Muscles*.—The musculature of the anterior abdominal wall is composed of two groups, the "flat muscles" (the external oblique, the internal oblique and the transverse) and the rectus muscles with the variable pyramidalis muscles. The muscle and aponeurotic fibers of the first group run transversely, and the muscle fibers of the second run vertically.

The oblique muscles are fanlike structures. The external oblique takes its origin from the anterolateral aspect of the lower eight ribs. The internal oblique originates mainly from the iliac crest. Superiorly the fibers of the external oblique muscle and aponeuroses run transversely, and inferiorly they assume a progressively oblique downward course. The aponeurotic fibers of the internal oblique muscle run transversely in the lower part of the abdomen and assume a progressively oblique upward course as they extend farther up the anterior abdominal wall. At no place in the anterior wall do the fibers of either oblique muscle deviate from the horizontal by more than 30 degrees. The transverse (transversalis) muscle is truly transverse. The aponeuroses of the three "flat muscles" enclose the rectus muscle as the rectus sheath and insert in the linea alba. Therefore the strong fibers of the rectus sheath assume the same general transverse direction as the muscle fibers they represent (fig. 1).

The rectus muscle is attached above to the anterior surface of the cartilages of the fifth, sixth and seventh ribs. Its upper attachment is three times as broad as its pubic insertion. Its lateral border at the costal margin may extend laterally as far as the anterior axillary line. Its medial border is separated from its fellow of the opposite side by the linea alba. The rectus muscle has three or four transverse fibrous intersections, called "lineae transversae." One is located at or near the umbilicus, while two more are equally spaced between this intersection and the origin of the muscle. If more than three are present, the others are distributed below the umbilicus. These fibrous intersections are tightly adherent to the anterior rectus sheath and limit its retraction when sectioned (fig. 2).

An incision of the abdominal musculature that parallels all of the fleshy and aponeurotic fibers causes the least structural and physiologic damage. An incision having this characteristic can be employed only if a small incision will suffice. The McBurney incision and the transverse midabdominal incision in which neither rectus muscle is sectioned are examples of this ideal type of incision. When larger incisions are needed, it becomes almost universally necessary to cut across either heavy muscle or aponeurotic fibers. It might appear theoretically better to sacrifice the fibers of the rectus sheath in order to save the rectus muscle. However, as a result of the lateral pull of the "flat muscles," retraction of the cut edges of the rectus sheath (or of the aponeuroses of the "flat muscle") always follows a vertical incision. Sloan⁹ devised a means of measuring this retraction and found that with the patient under light anesthesia a pull of 30 pounds (13.5 Kg.) was required to

12. Haight, C., and Ransom, H. K.: Ann. Surg. 114:243, 1941.

approximate the edges of a 3 inch (7.5 cm.) vertical incision. He also noted that the force necessary for approximation increased in proportion to the square of the length of the incision. Thus, a 5 inch (12.5 cm.) vertical incision requires a pull of 80 pounds (36.5 Kg.) to effect approximation. In a vertical incision the strong fibers of the aponeuroses (or rectus sheath) are cut transversely to their long axis, and in closing such an incision the sutures will parallel rather than transect strong fibers. This becomes of importance as one realizes that at rest there is a pull across this suture line of between 30 and 80 pounds (13.6 and 36.3 Kg.) and that this pull is increased considerably if the patient coughs or retches. In many instances the suture line fails to hold and eventration occurs. This is less likely to occur, however, if the aponeuroses are incised transversely, since then practically no pull is required to approximate their edges. This results because contraction

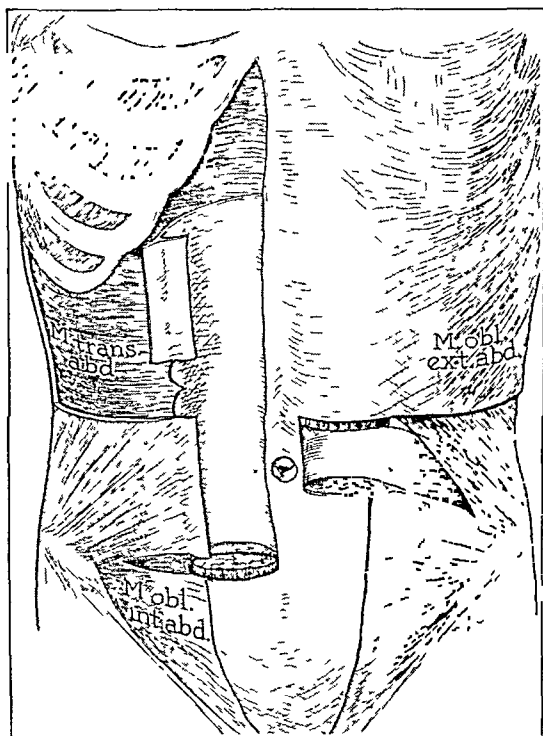


Fig. 1.—Drawing illustrating the muscles of the anterior abdominal wall and the formation of the rectus sheath from their aponeuroses. On the right is illustrated the origin of the external oblique and internal oblique muscles and the formation of the anterior rectus sheath above the linea semicircularis. The external oblique muscle contributes solely to the anterior sheath, while the internal oblique, in this location, contributes to both the anterior and the posterior sheath. In the lower left is illustrated the anterior rectus sheath below the linea semicircularis. Here the aponeuroses of the external and internal oblique muscles as well as the transverse muscle contribute to the anterior sheath. As illustrated on the left, the posterior rectus sheath is formed from part of the aponeurosis of the internal oblique muscle and from that of the transverse muscle. Note the relative transverse course of the aponeurotic fibers of the anterior abdominal muscles.

of the "flat muscles" will approximate rather than separate their own aponeurotic fibers. In addition, the closure of the transverse incision will be secure, because the sutures effecting approximation will pass across, rather than parallel, the heavy aponeurotic fibers.

Sectioning of one or both rectus muscles has no serious anatomic or physiologic sequelae. The muscles when healed will simply present an extratendinous inter-

section without functional impairment.¹³ These muscles should not be sectioned injudiciously, however, since frequently a short muscle-retracting incision will suffice. In view of the apparent absence of damage following sectioning of the rectus muscle, it is doubtful if it is justifiable to subject the patient to the increased trauma and operative time required for the large muscle-retracting incisions advised by Singleton¹⁴ and Sloan.⁹

3. *Blood Supply.*—The blood supply to the abdominal wall is abundant except at the linea alba. The main supply is derived from the superior and the inferior epigastric artery, which are branches of the internal mammary and the external iliac artery respectively. These vessels lie, for the most part, posterior to the rectus

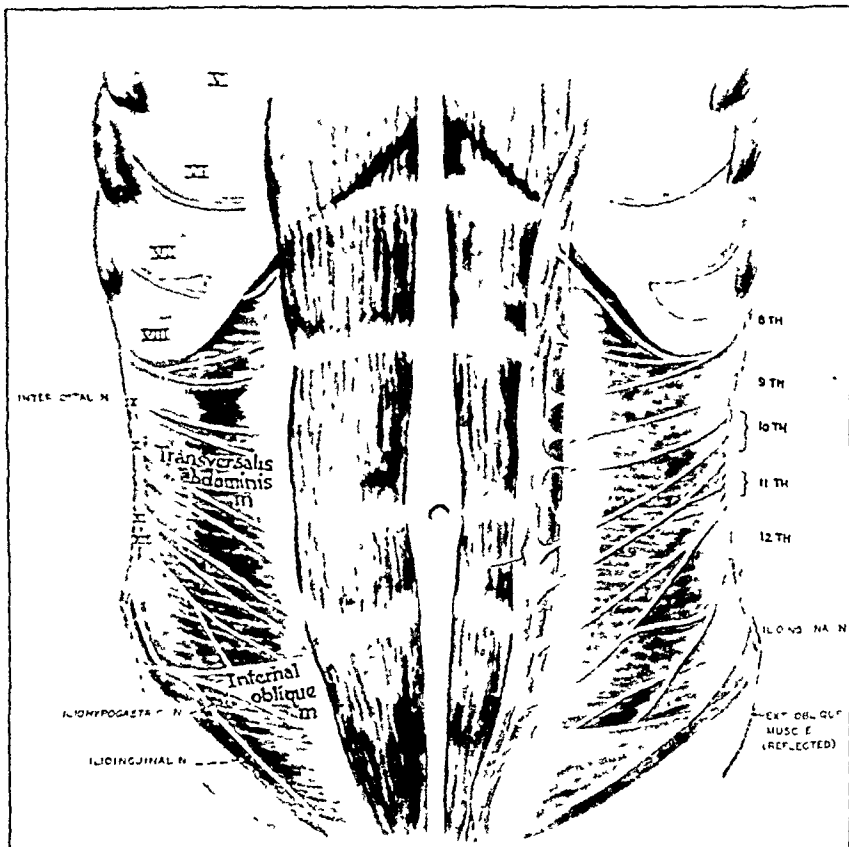


Fig. 2.—The nerves of the anterior abdominal wall and their relationship to the muscles. Note that many of the intercostal nerves are represented by more than one trunk and that there are frequent intercommunications. The rectus abdominis muscles are also shown with their transverse intersections.

muscle, where a rich anastomosis is formed. The remainder of the blood supply is derived from the deep circumflex iliac artery and from the lumbar and intercostal arteries. These also contribute to the anastomosis just mentioned. The transverse incision is undoubtedly more tedious to make, since it passes across a rich vascular bed. This same factor, however, serves to hasten healing of wounds and cannot necessarily be considered a disadvantage of the incision.

13. (a) Farr, R. E : *Journal-Lancet* 32:561, 1912; (b) in discussion on Meyer.¹⁶ (c) Moschowitz.⁶

14. Singleton, A. O. : *South Surgeon* 3:235, 1934.

4. *Innervation*.—The abdominal parietes derive their innervation from the lower six thoracic nerves and the first lumbar nerve. These nerves do not generally exist in single trunks as frequently described. Davies¹¹ has pointed out that the intercostal nerves, while still in the wall of the chest, exist as several branches (usually three) and not as single nerve trunks. These nerves frequently intercommunicate with neighboring intercostal nerves via a small branch that passes deep to the ribs. The intercostal nerves pass beneath the costal cartilages and enter the abdominal wall, usually as a single trunk. In the abdominal wall the nerves lie between the transverse muscle and the internal oblique muscle, where they form a free plexus.^{11a} Figure 2 illustrates the actual anatomic relationship and intercommunications between the larger branches of various intercostal nerves. A more complex intercommunication between the finer nerve fibers can be demonstrated by careful dissection. It is to be noted, especially on the right side of figure 2, that a majority of the nerves are represented by several trunks. It is possible to show that any one nerve in the anterior abdominal wall contains fibers from at least two, and sometimes three, intercostal nerves.^{11a} Furthermore, any one nerve at the lateral border of the rectus muscle is distributed to two segments of that muscle. Each myotonic segment is therefore supplied by at least two and possibly three, segmental nerves. This may well account for the fact that two and sometimes three intercostal nerves can be sectioned without noticeable damage.

The ninth intercostal nerves pass transversely across the abdomen at a point one third the distance between the umbilicus and the xiphoid process and this demarks the directional proclivities of the intercostal nerves. Nerves above this line tend to deviate upward, while those below deviate downward. When an incision is made lateral to the midline, the transverse variety is least likely to cause injury to the nerves. An incision in the upper part of the abdomen may be made obliquely downward and out without causing appreciable injury to nerves, while one in the lower part of the abdomen should be made obliquely upward and out. A vertical incision that passes through or laterally to the rectus muscle will enervate whatever tissue lies medially to it. As nerve tissue shows little tendency to regenerate, the enervated muscle is permanently damaged, and frequently atony and atrophy result.

TYPES OF TRANSVERSE INCISION

Variations in transverse incisions evolve principally around methods of dealing with the rectus muscles. Some (Singleton,¹⁴ Sloan⁹ and Mason¹⁵) have been reluctant to section even part of the rectus muscle and their incisions are directed at methods of obtaining the greatest exposure without sacrificing these muscles. Many others (Maylard,³ Boeckmann,⁴ Sprengel,^{5a} Bartlett and Bartlett¹⁰ and Moschcowitz⁶) have had no hesitancy to section the rectus muscles, and consequently their incisions are of simpler construction. In addition, many prefer to make their incisions slightly oblique rather than strictly transverse. Meyer¹⁶ has advocated a "flap incision" with the greater part of the incision in the transverse plane.

1. *Transverse Muscle-Retracting Incision*.—In making incisions of this type efforts have been aimed at saving the integrity of the rectus muscles. Anatomically and physiologically, such an incision would appear sound. However, its construction, in general, is time-consuming, and at best exposure is limited.

✓ 15. Mason, J. T.: New Abdominal Incision, *Arch. Surg.* **19**:129 (July) 1929.

16. Meyer, W.: *Ann. Surg.* **62**:573, 1915; Rectangular Flap Incision, *J. A. M. A.* **69**: 1677 (Nov. 17) 1917.

Singleton¹⁴ and Sloan⁹ have strongly advised this type of incision for work in the upper part of the abdomen. Sloan incises only the posterior rectus sheath and linea alba in a transverse plane. He prefers a midline vertical skin incision through which both anterior rectus sheaths are freed. This he follows with two vertical incisions, one through each anterior rectus sheath. Through these the rectus muscles are freed from their anterior sheaths and retracted laterally. The posterior sheaths of the muscles along with the linea alba are then sectioned in a transverse plane. Singleton has improved on this incision by approaching through a transverse cutaneous incision and by sectioning one of the anterior rectus sheaths transversely. Singleton and Sloan have claimed that that exposure is adequate for the average operation on the upper part of the abdomen. Others, however, feel that the exposure obtained is still inadequate and does not justify the increase in time needed for opening and closing such an incision. When a small incision in the upper part of the abdomen will suffice, it is advisable to make a midline transverse incision of all layers except the rectus muscles and retract these as conditions warrant.

The Pfannenstiel incision is the time-honored incision for pelvic operations. Owing to the altered construction of the rectus sheath in this region, a muscle-retracting incision is easier made. The rectus muscle, usually devoid of tendinous intersections in this region, is easily freed and retracted. Posteriorly, there is no true rectus sheath, only condensed properitoneal fat and peritoneum,^{11c} and this can readily be opened in any direction. If exposure is inadequate the rectus muscles can be sectioned without danger, preferably near their pelvic attachment, as advised by Cherney.¹⁷ If the incision is carried far laterally, it should be made obliquely upward and out along the course of the external oblique muscle. With a little care, the inferior epigastric vessels can be avoided.

2. Direct Transverse Incision of All Layers.—This is the incision of choice with most advocates of transverse incision. Those who oppose it do so usually on the grounds that it permanently injures the rectus muscle. It appears doubtful that this accusation is justifiable, since the literature is wanting in instances in which functional or anatomic impairment has resulted from transverse sectioning of the rectus muscles. Among those who have investigated this question, there is agreement that when healed the rectus muscle simply presents an extratendinous intersection without further damage. Farr^{13a} queried 30 users of transverse incision and was unable to locate a single incidence of sequelae directly resulting from sectioning of the rectus muscle. Among those who section the rectus muscle, there is also agreement to the fact that, if necessary, both rectus muscles can be sectioned without harm.

A transverse incision of this type may be made at any place over the anterior abdominal wall, though the site of election for laparotomy is usually 3 to 5 cm. above or below the umbilicus.¹⁸ A left-sided infraumbilical transverse incision gives excellent exposure to the sigmoid colon. For the upper part of the abdomen, Bailey¹⁹ prefers to use the ninth rib as a landmark and carries his incision entirely across the abdomen from one costal arch to the other. More commonly the incision is started just laterally to the midline and carried to the opposite costal arch. Depending on the needs, the incision may pass through one or both anterior rectus sheaths. The peritoneal cavity can now be opened through the linea alba and the round ligament of the liver ligated and sectioned. Moschcowitz⁶ and others have preferred to place hemostatic mattress sutures through the rectus muscle and rectus

17. Cherney, L. S.: Surg., Gynec. & Obst. **72**:92, 1941.

18. Gurd, F. B.: Canad. M. A. J. **42**:10, 1940. Bartlett and Bartlett.¹⁰ Moschcowitz.⁶

19. Bailey, H.: Tr. Internat. Coll. Surgeons **1**:158, 1938.

sheaths before sectioning the former. This, however, is not necessary, since the amount of bleeding is variable and can be controlled readily at the time of sectioning. Bleeding should be controlled by suture ligatures preferably incorporating a small piece of the rectus sheath, because ligatures or even suture ligatures will easily pull from muscular tissue. The peritoneal cavity can now be opened throughout the length of the incision. If the patient is hyperextended by means of a lift or by hyperextending the table, good exposure is afforded with a minimal amount of retraction. Closure of such an incision is greatly facilitated by flexing the patient. If this is done the incisional edge will approximate without tension. The first layer of sutures can be of chromicized catgut or interrupted black silk or cotton. It will approximate the peritoneum and the posterior rectus sheath, and where the incision extends far laterally it may approximate the peritoneum and the transverse abdominal muscle. Suturing of the rectus muscle is not only difficult and unsatisfactory but entirely unnecessary. When the anterior rectus sheath is approximated, the edges of the muscle will be in close proximity. The anterior rectus sheath should be closed with a nonabsorbable suture material, such as fine steel wire, cotton or silk. The muscle and aponeurotic layers lateral to the sheath should be closed with either fine cotton or silk. The subcutaneous tissue and skin can also be closed with fine silk or cotton. Recently we have been using two or three subcuticular steel wire sutures. These have been removed on the eighth or ninth day, and have given excellent results. Where drainage is indicated, it can be accomplished through the lateral borders of the incision. Retention sutures are unnecessary, but one may place reenforcing sutures through the linea alba, as this section of the incision will heal most slowly because of its poorer blood supply. The Bartletts¹⁰ prefer to stagger the various layers of the abdominal wall as they are incised and have contended that a stronger closure is effected if the sutured layers are not all in the same plane of section. It is questionable whether this slight increase in strength justifies the extra time required.

3. *Oblique Incision*.—When there is a narrow costal arch, access to the upper part of the abdomen can be facilitated by using an oblique incision. The obliquity can be varied to meet the needs at hand, but the nearer it approaches the transverse plane the better will be its structure and its physiologic qualities. An incision of the Kocher type, which lies close to and parallel to the costal arch, is to be condemned, because it sections too many nerves. All layers of the abdominal wall may be sectioned in the plane of the cutaneous incision, but a stronger closure is possible if the two oblique muscles lateral to the rectus sheath are sectioned along the course of their fibers. Singleton²⁰ has advised an oblique lateral abdominal incision in which the rectus muscle is retracted medially. His incision extends from a point 3 to 4 inches (7.5 to 10 cm.) above the umbilicus down to a point just posterior to the anterior superior spine of the ilium and slightly above the iliac crest. The rectus muscle is freed and retracted medially. Such an incision undoubtedly sections the ninth, tenth and eleventh intercostal nerves and for that reason cannot be favored for general usage. If the rectus muscle were sectioned adequate exposure could be obtained through its medial portion without carrying the incision far into the flank; thus its chief drawback would be avoided. An oblique incision affords unusually good exposure of the biliary system with the least amount of retraction. A similar incision on the left gives equally good access to the spleen, and if it is extended to include part of the right anterior and posterior rectus sheaths good access is afforded to the stomach also. An oblique incision in

20. Singleton, A. O., and Blocker, T. G., Jr.: Problem of Disruption of Abdominal Wounds and Postoperative Hernia, *J. A. M. A.* **112**:123 (Jan. 14) 1939.

the lower part of the abdomen should follow the fibers of the external oblique muscle or aponeuroses; such an incision affords good exposure to peritoneal as well as extraperitoneal structures located in this region. The suprapubic curvilinear incision as used by Judd has proved to be an excellent incision for repair of bilateral inguinal hernias (fig. 3).

4. *Flap Incision.*—Meyer,¹⁰ who was a strong advocate of transverse incisions, pointed out that when exposure proves inadequate with a transverse incision an extension can be carried either up or down in the medial portion of the rectus sheath, thus making a rectangular flap. This procedure can be used in place of an oblique incision when the costal arches are steep. The longitudinal portion of the incision should be as short as possible, since this is its weakest part. A flap incision

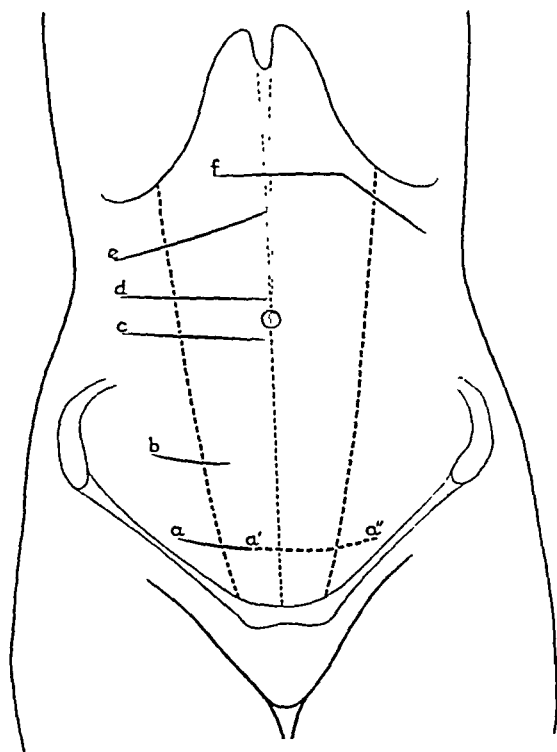


Fig. 3.—Common locations for transverse incision: *a-a'*, unilateral inguinal herniorrhaphy incision; *a-a''*, incision used for bilateral inguinal herniorrhaphy; *b*, Davies^{11a,b} or Rockey (*S. Clin. North America* 4:1205, 1924) appendectomy incision; *c*, laparotomy incision especially valuable in cases of intestinal obstruction (similar incision on the left gives good exposure of sigmoid colon); *d*, incision used for right colectomy; *e*, incision giving good access to biliary system (similar incision on the left used for splenectomy); *f*, incision used for gastric operations.

is more difficult to close than a strictly transverse or oblique type, and this difficulty increases as the longitudinal portion lengthens. The possibility of a "flap incision" should nevertheless be kept in mind, since it frequently proves a helpful adjunct to a transverse incision.

CLINICAL ADVANTAGES OF THE TRANSVERSE INCISION

Complications of laparotomy, such as evisceration, incisional hernia and abdominal adhesions, frequently constitute a more serious and difficult problem than the original operation. Singleton²⁰ in an exhaustive survey reported disruption

to have a frequency varying from 0.6 to 3 per cent and to carry a mortality of between 25 and 40 per cent. (Others list mortality rates as high as 75 per cent.) In 3,147 anatomic incisions (transverse or oblique) he found only 1 disruption, or an incidence of 0.03 per cent.

In an even greater number of incisions, disruption starts in the deeper layers but fails to be complete, and an incisional herniation develops. Sloan,⁹ investigating vertical incisions, found that of those 5 inches (12.5 cm.) or more in length and of ten years' duration, 80 per cent showed evidence of herniation or weakness. A survey of the literature reveals an incidence of postoperative incisional hernias of from 2 to 10 per cent. Mason,¹⁵ reporting on a large series from the Mayo Clinic, showed that 10.8 per cent of all herniorrhaphies were done to repair abdominal incision. This is of greater significance as one realizes that many incisional hernias go unrepaired and even undiagnosed. Incisional hernias are rare in transverse incisions, and the few that do occur are almost universally the end results of a badly infected incision. Coryllos, as quoted by Farr,^{13a} studied 2,855 transverse incisions and found only 7 postoperative hernias, not one of which followed primary healing. This gave an incidence of 0.27 per cent in the cases in which there was suppuration and none in the cases of clean wounds. Similar results were found on analyzing 1,542 cases, including some of those reported by the more recent advocates (Moschowitz,⁶ Wanscher,²¹ Boeckmann,⁴ Hesselgrave,²² Sprengel,^{5a} Lynn and Hull,²³ Saunders²⁴ and Singleton²⁰). In this series only 2 hernias were reported, both in badly infected wounds. This gives an incidence of only 0.13 per cent. With the 225 consecutive transverse incisions in the upper part of the abdomen studied at the University of Michigan Hospital, only 1 herniation was encountered, and this was a small omental hernia at the site of drainage. It had no clinical significance and was found only after careful check-up examination.

This low incidence of evisceration and herniation is the direct result of the stronger closure effected in transverse incision. The edges of a transverse incision tend to approximate by themselves, and the sutures that effect this closure insure a firmer incision because they transect the stronger aponeurotic fibers of the abdominal wall. In closing vertical incisions difficulty is frequently encountered in closing the peritoneum and the posterior rectus sheath. Weakness of this closure, aside from favoring evisceration and herniation, also serves as a nidus for the development of abdominal adhesions. As many²⁵ have pointed out, adhesions are less frequent in transverse incisions. The value of this is better appreciated when it is realized that adhesions are the most common causative agents of acute intestinal obstruction and that this condition carries a mortality rate of about 26 per cent.²⁶ Aside from this, countless other patients present minor complaints which are generally assumed to be the result of adhesions.

Pulmonary atelectasis and pneumonia remain the most important causes of early postoperative complications. Especially is this so with operations on the upper part of the abdomen, which have these complications in from 5 to 12 per cent of the cases.²⁷ With the series of transverse incisions in the upper part of the abdomen

21. Wanscher, O., cited by Boeckmann.⁴

22. Hesselgrave, S. S.: *St. Paul M. J.* **12**:531, 1910.

23. Lynn, F. S., and Hull, H. C.: *Ann. Surg.* **104**:233, 1936.

24. Saunders, R. L.: *South. Surgeon* **6**:365, 1937.

25. McArthur, L. L.: *Surg., Gynec. & Obst.* **20**:83, 1915. Farr,^{13a,b} Moore.⁸

26. Boyce, F. F., and McFetridge, B. M.: *South. Surgeon* **6**:109, 1937.

27. Jones, D. F., and McClure, W. L.: *Surg., Gynec. & Obst.* **51**:208, 1930.

studied at the University of Michigan Hospital, there were no deaths attributable to pulmonary complications, and the incidence of these complications was only 2.6 per cent (table). This low percentage is of greater significance if compared with the incidence of 9.5 per cent for vertical incisions as reported by Haight and Ransom¹² from the same hospital. In a similar series of 125 cases reported by Jones and McClure²⁷ there were no cases of atelectasis or pneumonia, but there were 5 cases of pulmonary emboli, 2 of which were fatal. Haight and Ransom¹² have pointed out that decreased respiratory and cough efficiency are important causative factors of these complications. A vertical incision passing through or laterally to a rectus muscle will injure the intercostal nerves to that region. These sectioned nerves are hyperirritable during the early postoperative course. In the patient's subconscious effort to minimize pain, the abdomen is splinted. As a consequence, diaphragmatic excursions are impaired, and a decrease in vital capacity and tidal air results. Beecher²⁸ has reported this reduction to be as much as 58 per cent. This decreased ventilation favors the development of anoxia and patchy atelectasis (postoperative bronchopneumonia). Also when a vertical incision has been used coughing not only endangers the incision but is very painful. This is

Comparative Study of Pulmonary Complications Following Transverse and Vertical Incisions

Number of cases	Type of Incision	
	Transverse	Vertical
	225	346
Patchy atelectasis	5 (2.2%)	26 (7.5%)
Massive atelectasis	0	5
Pleuritis	0	1
Infarct or embolism	1	1
Total pulmonary complications	6 (2.6%)	33 (9.5%)
Pulmonary complications chief cause of death	0	3
Pulmonary complications contributing cause of death	0	1

important in view of the fact that coughing has proved to be one of the most important physical means of preventing postoperative complications. The reduction of postoperative pain and the stronger closure afforded by transverse incisions, aside from being heartily welcomed by the patient, allow for earlier and greater activity with resulting reduction in pulmonary hypostasis. This reduction of hypostasis, along with the betterment of the respiratory and cough efficiency, serves to retard the incidence of pulmonary complications.

Transverse incision in many instances allows for better and easier exposure. This is especially so in operations on the gallbladder, because the incision approaches the operative field more directly. For operations on the upper part of the abdomen a transverse incision need not extend into that portion of the celomic cavity where the greater portion of the small intestine lies. This practically eliminates this structure from the operative field. Thus easy exposure is accomplished without repeated packing and manipulation of the small intestine. Hyperextension of the patient will further aid exposure and facilitate operation. This helps reduce trauma and favors a smoother postoperative course. The little extra time needed to make transverse incisions is usually more than offset by that ultimately saved as a result of improved exposure.

The narrow, firm cicatrix, the reduction of postoperative pain, the absence of incisional neuromas²⁹ and the shorter period of hospitalization are all factors greatly appreciated by the patient. A patient with a transverse incision can, if conditions warrant, be allowed up with relative safety almost as soon as he has recovered from the anesthetic. Usually, however, a patient who has had an operation on the upper part of the abdomen is not allowed out of bed until the seventh postoperative day. This reduces the average hospitalization period, as required with vertical incision, by five to ten days. A person requiring operation should be entitled to every comfort compatible with good therapy, and in the case of abdominal operation it would seem that frequently this can best be accomplished through the use of a transverse abdominal incision.

SUMMARY

The transverse abdominal incision is based on sound anatomic, physiologic, and clinical principles. This incision parallels the lines of skin cleavage, the heavier muscular and aponeurotic fibers and the greater portion of the nerves of the anterior abdominal wall. As a result of the stronger incisional closure thus afforded, there are fewer eviscerations, herniations and abdominal adhesions.

The incidence of pulmonary complications found after 225 consecutive transverse incisions in the upper part of the abdomen was 2.6 per cent, which is considerably below the 9.5 per cent for a comparable series of vertical incisions.

The virtual absence of incisional pain, the narrow, firm cicatrix and the average reduction of from five to ten days in the period of hospitalization are attributes of the transverse incision worthy of consideration.

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29. Bancroft, F. W.: Painful Postoperative Abdominal Scars, *Arch. Surg.* **21**:289 (Aug.) 1930.

PRIMARY INTRACRANIAL LYMPHOSARCOMA

A REPORT OF TWO CASES AND REVIEW OF THE LITERATURE

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In the past half-century pathologists have learned to recognize tumors arising from lymph nodes and other lymphatic structures in nearly every organ and structure of the body; however, so far as we can determine, the skull and intracranial dura mater have not been indicated as the primary site of origin of lymphosarcoma.¹ Therefore, there is adequate cause for reporting 2 cases in which the primary focus appears to have been in the intracranial dura mater or possibly in the overlying cranial bone.

REPORT OF CASES

CASE 1.—A white man, aged 24 years, came to the Mayo Clinic in August 1926, because of symptoms of an intracranial lesion. Two years before this, he had been struck by a baseball in the right parietal region but had not lost consciousness. There were no symptoms from this nor any other symptoms until four months before the patient came to the clinic, at which time he noticed a small, hard lump at the site of the old injury. Although there was a slowly progressive increase in the size of this tumefaction, constant severe frontal headaches began only two weeks before his registration. These bouts of headache were followed by attacks of motor and sensory paresis of the left hand, progressing up the arm into the left side of the face and chest. In addition, there had been several similar attacks with "thickness of speech." Severe vomiting had occurred during the previous two days.

A thorough physical examination did not disclose any infectious process or neoplasm elsewhere in the body. The neurologic examination revealed cloudiness of the sensorium, so that the patient was mentally dull and confused. There was evident central paresis of the left half of the face and the left upper extremity. Examination of the scalp disclosed the swelling in the right midparietal region to be tender, smooth, firm and not movable with the scalp. It was elevated about 1 cm. and was about 3 to 4 cm. in diameter. A meningioma with hyperostosis in the right parietotemporal area was suspected, although roentgenograms of the head were reported not to show evidence of it and recent review of them has confirmed this.²

Exploratory craniotomy was performed a few days after the patient's admission to the hospital. The operation disclosed a malignant tumor arising from the dura (9 by 8 by 3 cm.), eroding it and the overlying portion of the skull (5 by 4 by 8 cm.) on the right side. After removal of most of the tumor, a wide gap in the skull was left and the wound closed. The patient survived the operation for nine days, having slowly failed, with hyperthermia and tachycardia.

Section on Neurologic Surgery of the Mayo Clinic.

Abridgment of part of a thesis submitted by Dr. Abbott to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of M.S. in Neurosurgery.

1. We are familiar with lymphosarcoma whose primary focus is within the orbit and which by subsequent extension comes to involve the intracranial dura mater, but it is not our purpose to discuss this problem. It is our impression that the primary symptoms produced by this and other forms of sarcoma of the orbit are referable to the involved orbit and that these forms of sarcoma can be diagnosed as such; thus, they need not be confused with the type here under consideration.

2. Roentgenograms of the preserved bone flap were made recently and disclosed only slight evidence of the infiltrative process.

A complete necropsy, performed two and a half hours after death, was permitted, which, aside from the intracranial lesion, disclosed minimal lesions of both healed and active pulmonary tuberculosis, which would have been difficult to ascertain clinically. Also there were horseshoe kidneys, leukoplakia of the esophagus and mild (benign) hyperplasia of the lymph follicles of the intestine.

Examination of the intracranial dura mater revealed the operative defect to be surrounded by an irregular rim of tumorous tissue 2 to 5 cm. wide. On gross inspection this was identical with the operative specimen, although not as thick.

Microscopic study of sections made from the tumorous mass in the dura mater showed that it was partially surrounded by a fibrous capsule, thin strands of which extended down into it and by branching formed a fibrous trabecular framework. It was an extremely cellular tumor composed principally of two types of cells; those most abundant were small lymphocytes that had hyperchromatic nuclei and scanty cytoplasm and whose outlines were not too well defined. Nucleoli were present in many, but not all, of the nuclei. There were a great many mitoses throughout the neoplasm, which added to its highly malignant character. About a third of the cells had larger, pale-staining, irregular and indented nuclei with cytoplasm varying in amount and occasionally without discernible cell boundaries. The

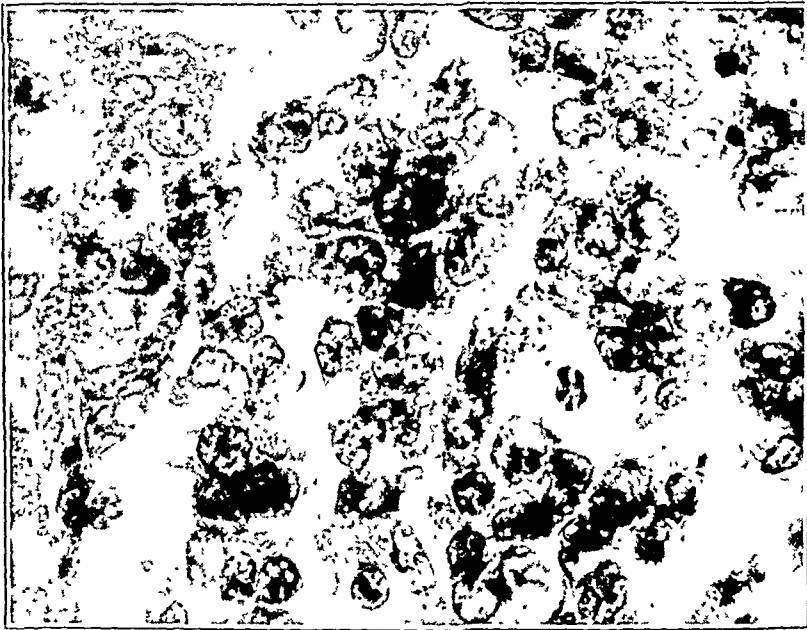


Fig. 1 (case 1).—Lymphosarcomatous cells (hematoxylin and eosin $\times 900$).

chromatin appeared in these to be collected in fine strands and minute dots, and nucleoli of varying sizes were found more frequently than in the first type but in no constant position in the nucleus. Mitoses, although present, were not as frequent as in the smaller, darker, lymphocyte-like cells (fig. 1).

There were occasional large (giant) cells, usually stained very pale, appearing as distinct, dark, thin rims (nucleus) with fine strands of chromatin extending toward the center. An eccentric nucleolus could be seen occasionally inside these huge giant cells. Fairly frequently thin rims of irregular cytoplasm, at times of stellate outline, were encountered. These, as well as the previously described pale cells, were taken to represent the so-called reticulum cells seen in normal lymphatic structures, which here had entered into the formation of the tumor to a minor degree.

The silver-impregnated sections were not of additional aid except in detecting reticulin, which was present along the blood vessels, in the connective tissue trabecula dispersed through the tumor and also as fine intercellular fibrils. Glial cells, nerve cells or their processes were not present in any of the sections.

Sections taken through the underlying leptomeninges and cortex were of interest in that the subarachnoid space was filled with the small lymphocyte-like cells and the pia and arach-

noid were likewise infiltrated. The vessels, where pulled away from the surrounding structure, were covered with a layer of these cells and could be followed for 2 to 3 mm. on into the cortex in the pial funnel and Virchow-Robin spaces; here they appeared as well formed perivascular cuffs without invading the nerve tissue (fig. 2). This was obviously an infiltration process and not a primary propagation, such as is seen in the perivascular sarcomas.

There were minor changes in the nerve tissue subjacent to the tumor as evidenced by a minor degree of gliosis and edema (gemastete glia cells; swollen and increased numbers of oligodendroglia and microglia cells).

The infiltrative process in the bone was entirely osteoclastic; thus the small hyperchromatic cells were present in the haversian canals and in lacunas and irregular eroded channels. Although the skull was thickened, there were but few tumor cells exterior to the outer table. The greatest erosion was of the inner table, as though the neoplasm had originated in the dura and extended into the overlying portion of the skull (fig. 3a).

A diagnosis of lymphosarcoma involving the dura mater, skull and leptomeninges with perivascular cortical invasion was made. The possibility of this tumor's being Hodgkin's disease was ruled out by the absence of Dorothy Reed cells and other evidences of Hodgkin's disease.



Fig. 2 (case 1).—Lymphosarcoma in the subarachnoid space and extending into the brain by means of the perivascular spaces (hematoxylin and eosin $\times 55$).

Comment on Case 1.—The question in this case is not of the identity of the tumor or the possibility of metastasis; both are well answered in the thorough necropsy and study of the sections which identified the growth as a lymphosarcoma without any evidence of tumor elsewhere in the body. The question is: Did the tumor arise in the skull or in the dura mater? This can be answered partially by pointing to the erosion of the inner table as compared with the minor involvement of the outer table and the presence of the major part of the tumor in the dura mater. It is recognized that the dura mater does not contain any lymphatic structures. The same is, of course, true of the leptomeninges and the nervous system; however, it may or may not be of significance to point out that any infection or injury does call forth an abundance of lymphocytes into the injured dura mater. This patient did have a previous injury to the skull, although of a minor nature. If one may theorize, might it be possible that a focus of lymphocytes in the dura mater was

thus formed from which the neoplasm may, in some unknown manner, have become malignant? Nevertheless, the possible origin in the skull itself cannot be disregarded; neither can it be proved. Such seems to have been the situation in the case reported by Bassoe,³ except that the tumor was obviously metastatic. In discussing this case, Phemister suggested that the tumor metastasized to the skull and then extended into the dura mater, but he noted the extensive erosion of the inner table and mentioned that metastasis to the dura and subsequent infiltration of the overlying bone seemed more probable. With essentially the same reasoning, one may well argue that the tumor in case 1 originated in the dura mater and spread into the skull.

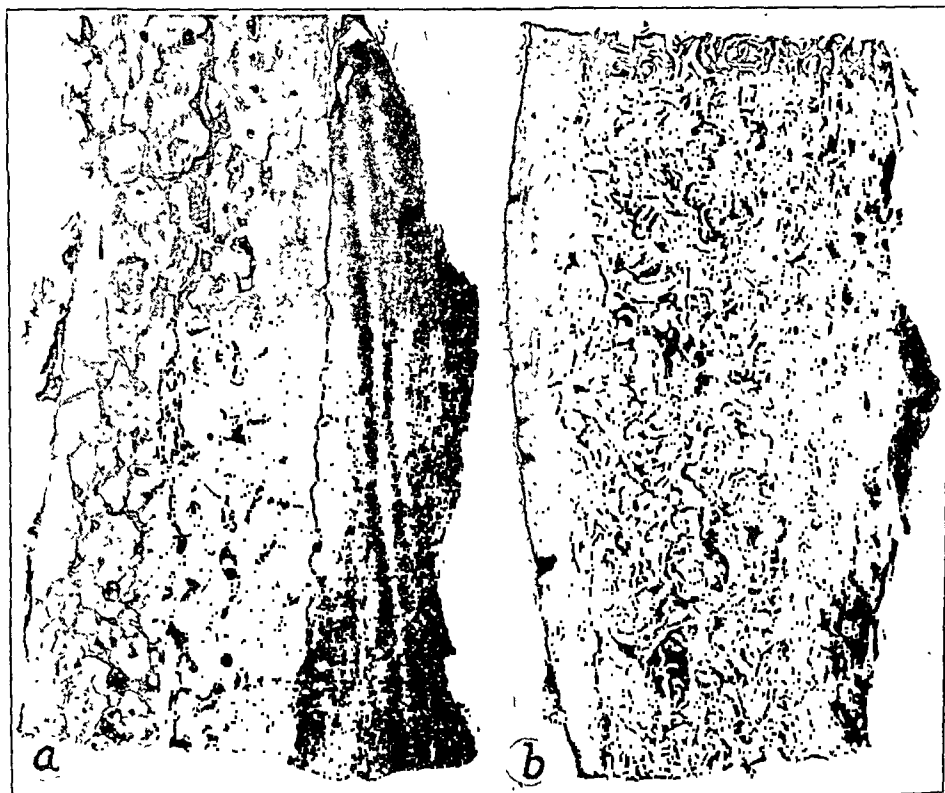


Fig. 3.—Lymphosarcoma involving skull and dura mater. Sections of skull: *a*, case 1, and *b*, case 2. Note erosion of inner table and presence of tumorous mass in both *a* and *b*; however, in *a* the outer table also is slightly involved with a few small tags of tumor present in the subaponeurotic region. It is not certain whether the primary site was in the dura mater or in the skull (hematoxylin and eosin $\times 5\frac{1}{2}$).

The following case is similar to case 1 but regrettably necropsy was not obtained. Nevertheless, since the case is so unusual and of equal importance, it is here described.

CASE 2.—A white woman, aged 57 years, registered at the clinic on Feb. 3, 1926, complaining of malaise, anorexia, dizziness, headaches and difficulty in walking, which had been present since May 1925. Roaring in the ears, mostly on the right, on lying down had begun in October. About six months previous to her entry at the clinic, she had noted a persistent "lump" in the left frontoparietal region. For four months, numbness and paresthesias of

3. Bassoe, P.: Tumor-Like Infiltration of Cerebral Dura: A Case of Lymphosarcoma with Clinical Picture of Hodgkin's Disease, *Arch. Neurol. & Psychiat.* 7:788-790 (June) 1922.

the right finger tips had been noted, but previous to this (since November 1925) she had had monthly attacks of paresthesias of the right finger tips, lasting from fifteen to twenty minutes. Vision had been poor for two months and the defect had been associated for six to eight weeks with diplopia.

The examination revealed a somewhat confused middle-aged patient who had moderate arteriosclerosis but was without neurologic lateralizing signs. The swelling in the left frontoparietal region of the scalp was only slightly tender, firm and rounded (dome-shaped) and seemed attached to the skull. It was elevated about 1 cm. and was 3 or 4 cm. in diameter. The spinal fluid gave positive Wassermann and Nonne reactions. A diagnosis of syphilis of the central nervous system was made, and appropriate treatment instituted. The tumefaction in the frontoparietal region of the scalp was taken at first to be a gumma, but it did not respond to antisypilitic treatment; thereupon an osteomatous nature was assumed (on roentgenographic interpretation) and the patient was allowed to go home, with instructions to return to the clinic in September of the same year.

On the patient's return there was evidence of an increased intracranial pressure, and, in view of the mass in the left frontoparietal region of the scalp, a flap was turned down over this area on Oct. 6, 1926. An osteomatous nodule was found adherent to the dura. On the medial aspect of the dura at this point was an extensive mushroom-like neoplasm extending out over the temporoparietal area. A portion of the tumor and of the bone flap was removed. Postoperatively, roentgen therapy was administered, with some improvement of the patient's symptoms.

The surgical specimen was reported as chronic inflammatory tissue, and it was not until the patient returned, in December 1927, because of left cervical adenopathy which definitely appeared to be extending down through the scalp from the operative site into the cervical chain of lymph nodes, that the correct diagnosis was made by means of removal of a cervical lymph node for biopsy. Subsequently, heavy roentgen therapy to the glands of the neck and the cerebral lesion relieved the most distressing lymphedema of the left side of the face.

The patient returned to the clinic on Oct. 24, 1928, because of a gradual return of the "lump in the neck," edema of the left side of the face and bulging in the cranial decompression wound. Examination substantiated her observations and also disclosed numerous tiny shotlike lymph nodes in both sides of the neck. More roentgen therapy was instituted and she again showed some improvement. She returned home and was not heard of until by chance her death was reported. Death occurred on Oct. 25, 1932, about six years after her operation. This was confirmed by her family physician.

Sections were made of the tumorous mass, including the grossly infiltrated bone flap, and were stained with hematoxylin and eosin and by Mallory's phosphotungstic acid and Perdrau's silver impregnation methods.

Histologic investigations disclosed that the cells comprising this tumor were of three types, not including the occasional giant cells to be mentioned later. The majority were ovoid to polyhedral; they possessed a scant to moderate amount of bluish to pink-staining cytoplasm. The nuclei, although somewhat vascular, contained more chromatin than those of ordinary lymphocytes and rarely contained visible nucleoli. Cellular pleomorphism was only moderate, and mitoses were not overly abundant. Tumor giant cells were rarely encountered but when present contained single, bulky, hyperchromatic nuclei, in most cases filling nearly all of the cell. Cells of a second type, considerably larger than the cells of the small lymphocytic type, were present but fewer than the others and were characterized by their much lighter staining, indented or kidney bean-shaped nuclei containing only tiny rods of chromatin; their cytoplasm stained much lighter and its bounds were at times indistinct. These probably represented the reticulum cells and were scattered among the tumor cells without any definite pattern or evidence of their function, or evidence of their playing the major role in the formation of this tumor. They were, however, a little more numerous than in normal lymph structures. Cells of the third type appeared to be the fibroblasts and were present in the fibrous trabecula of the neoplasm.

Reticulin was demonstrated intercellularly and independent of cellular arrangement and in the fibrous trabecula. Collagen was in the bands and strands which made up the stroma of connective tissue.

The giant cells were not of the Dorothy Reed type and there were no eosinophils present; therefore, this was not Hodgkin's disease. Neither was there evidence of syphilitic gummas from which a lymphosarcoma might have arisen.

The decalcified sections made of the infiltrated bone flap disclosed that its moth-eaten appearance was due to tumor tissue infiltrating in the haversian canals and in newly formed channels resulting from an osteoclastic process (figs. 3 *b* and 4 *a* and *b*). The lymphosar-

comatous cells were thus present in the outer table of the skull, and a very few were situated subperiosteally. The greatest degree of destruction was on the inner surface. Reticulum cells were distributed among the smaller lymphocytic type of cells in about the same frequency as in the intracranial portion of the tumor. The infiltrative process was entirely osteoclastic; there was no evidence of any osteoblastic activity. A diagnosis of lymphosarcoma involving the skull, dura mater, leptomeninges and brain was made.



Fig. 4 (case 2).—Lymphosarcoma—small cell type. In *a*, tumor cells have infiltrated the dura mater and are seen on both its internal and its external surface (hematoxylin and eosin $\times 65$). In *b* is shown involvement of the skull. Tumor cells are present in the haversian canals and in newly formed channels resulting from an osteoclastic process. The tumorous mass seen at the right was continuous with the intracranial (dura) tumorous mass (hematoxylin and eosin $\times 60$).

Comment on Case 2.—From the microscopic study there was no definite evidence of the origin of this neoplasm, but in view of the greater erosion of the inner table and the presence of a large dural mass which infiltrated the brain, the evidence appeared to be in favor of its dural origin. Numerous repeated examinations had failed to show evidence of any primary lesion outside of the dura and skull. The spread of metastatic growths was seen to come from the operative site downward into the cervical lymph nodes. Thus this neoplasm appears to have been primary in the dura mater or the skull.

GENERAL COMMENT

Undoubtedly Virchow⁴ had a fair comprehension of the lymphomas and lymphoblastomas and probably of lymphosarcoma, as can be discerned from the excellent description given in his "Die krankhaften Geschwülste" in 1863. However, it remained for Dreschfeld⁵ in 1891 and Kundrat⁶ in 1893 to identify one malignant type clearly. Kundrat chose to call this type "lymphosarkomatosis." Following this, other tumors of the lymphatic structures were recognized by Becker⁷ in 1901 (giant follicular hyperplasia⁸—Brill-Symmers' disease), by Ciaccio,⁹ by Goormaghtigh,¹⁰ by Oberling¹¹ (reticulum cell sarcoma), by Parker and Jackson¹² and by Edwards¹³ (reticulum cell sarcoma of bone). Prior to these disclosures Hodgkin's disease became well known, and its involvement of the nervous system was recognized by Murchison and others.¹⁴ Yet after at least a half a century the etiology of these neoplasias remains obscure.

4. Virchow, R.: *Die krankhaften Geschwülste*, Berlin, A. Hirschwald, 1863, vol. 1, p. 543.

5. Dreschfeld, J.: Ein Beitrag zur Lehre von den Lymphosarkomen, *Deutsche med. Wchnschr.* **17**:1175-1177 (Oct. 13) 1891.

6. Kundrat: Ueber Lympho-Sarkomatosis, *Wien. klin. Wchnschr.* **6**:211-213 (March 23); 234-239 (March 30) 1893.

7. Becker, E.: Ein Beitrag zur Lehre von den Lymphomen, *Deutsche med. Wchnschr.* **27**:726-728 (Oct. 17) 1901.

8. Brill, N. E.; Baehr, G., and Rosenthal, N.: Generalized Giant Lymph Follicle Hyperplasia of Lymph Nodes and Spleen: A Hitherto Undescribed Type, *J. A. M. A.* **84**:668-671 (Feb. 28) 1925. Symmers, D.: Follicular Lymphadenopathy with Splenomegaly: A Newly Recognized Disease of the Lymphatic System, *Arch. Path.* **3**:816-820 (May) 1927.

9. Ciaccio, C.: Ueber einen Fall von Synzytium-Endotheliom der Lymphdrüsen mit Studien und Betrachtungen über die Endothelien und Endotheliome der Lymphorgane, *Virchows Arch. f. path. Anat.* **198**:422-448 (Dec. 4) 1909.

10. Goormaghtigh, N.: Sur la prolifération maligne du tissu réticulo-endothélial des ganglions lymphatiques, *Compt. rend. Soc. de biol.* **92**:457-458 (Feb. 20) 1925.

11. Oberling, C.: Les réticulosarcomes et les réticulo-endothéliosarcomes de la moelle osseuse (sarcomes d'Ewing), *Bull. Assoc. franç. p. l'étude du cancer* **17**:259-296 (May) 1928.

12. Parker, F., Jr., and Jackson, H., Jr.: Primary Reticulum Cell Sarcoma of Bone; *Surg., Gynec. & Obst.* **68**:45-53 (Jan.) 1939.

13. Edwards, J. E.: Primary Reticulum Cell Sarcoma of the Spine: Report of a Case with Autopsy, *Am. J. Path.* **16**:835-844 (Nov.) 1940.

14. C. Murchison (Case of "Lymphadenoma" of the Lymphatic System, Liver, Lungs, Heart and Dura Mater, *Tr. Path. Soc. London* **31**:372-389, 1869-1870) was the first to describe the involvement of the intracranial dura mater by a lymphoblastoma, but his patient probably had Hodgkin's disease rather than lymphosarcoma. The same is true of the lymphomatous growth in the dura with erosion of the base of the skull reported by Roncalli in 1892 (Roncalli, F.: *Sarkom des Nasenrachenraumes*, 1 Fall, *Jahresb. ü. d. chir. Abt. d. Spit. in Basel*, 1894, p. 19). Guillaín, Alajouanine and Périssou (Lymphosarcome extra-dural métastatique ayant déterminé une compression médullaire d'apparence primitive, d'évolution rapidement progressive; laminectomie; extirpation et radiothérapie; guérison, *Bull. et mém. Soc. méd. d. hôp. de Paris* **49**:1057-1061, 1925) in 1925 claimed to be the first to report involvement in the spinal cord (dura) by lymphosarcoma. Jacod's studies in 1914 (Jacod, M.: *Sur les sarcomes de la trompe d'Eustache cartilagineuse*, *Rev. de laryng.* **2**:169-179, 1914) and later are also of importance, since they pertained to lymphosarcoma at the base of the skull.

Involvement of the nervous system by lymphosarcoma has been described by many writers but always as a metastatic or direct spread from nearby structures. In lymphosarcoma in the head, the structures at or near the base of the skull are frequently the site of origin. Sugarbaker and Craver,¹⁵ in analyzing the records of 196 cases in which the diagnosis was confirmed by biopsy, found that in approximately two thirds of their cases the lesion began in lymph nodes and in a third it was of extranodal origin; in two thirds (65 per cent) of the latter group the initial lesion was in the "head structures"¹⁶ but outside the cranial vault. Of the 196 cases there were only 4 instances of involvement of central nervous system tissue (brain, 1 case; spinal cord, 3).

A survey of the literature pertaining to lymphosarcoma, however, reveals a much greater frequency of neurologic symptoms than the foregoing statistics indicate;¹⁷ a few of the reports seem worthy of review here. As far as we are aware, Woltman¹⁸ was the first to review the literature and report a fair-sized series in which there were intracranial complications of lymphosarcoma;¹⁹ however, previous to his report and since then many casual reports of involvement of the central nervous system and the cranial nerves have appeared. In tabulating the neurologic manifestations, it is apparent that they can be divided into the following anatomic groups: (1) extracranial or subcranial, (2) intracranial and (3) intraspinal (dura mater). We are here concerned only with the first two groups.

The first group is of interest in that the cranial nerves, making their exit through the basilar foramina, may be interrupted by pressure or by invasion of tumor cells. The majority of the observations fall into this group; at least this is true from clinical observations, for there are few reports of either surgical or morbid anatomy of lymphosarcomatous invasion of the nervous system and its envelopes.

It has been emphasized frequently that the symptoms in this group are produced commonly by tumors attacking the posterior cervical chain of lymphatics, causing extracranial lesions, although this rarely may be due to their local intracranial extension. These lesions give rise to irritative or paralytic symptoms from the last four cranial nerves and the cervical sympathetic nerves, thus producing the several well known syndromes (the syndromes of the posterior lacerated foramen or jugular foramen [Vernet²⁰]; condylojugular foramina [Collet²¹ and Sicard²²];

15. Sugarbaker, E. D., and Craver, L. F.: Lymphosarcoma: A Study of One Hundred and Ninety-Six Cases with Biopsy, *J. A. M. A.* **115**:17-23 (July 6) 1940.

16. Tonsils, 14 per cent; nasopharynx, 5 per cent; parotid gland, 1 per cent; antrum, 1 per cent; orbit, 0.5 per cent; eyelids, 0.5 per cent (based on the entire group [196 cases]).

17. In a survey of the clinical and pathologic problems in this connection C. Davison and J. J. Michaels (Lymphosarcoma with Involvement of the Central Nervous System, *Arch. Int. Med.* **45**:908-925 [June] 1930) reported 7 cases in which there were neurologic symptoms out of 26 cases of lymphosarcoma, in all of which the growths clinically belonged in the first group, subsequently described in the text.

18. Woltman, H. W.: Malignant Tumors of the Nasopharynx with Involvement of the Nervous System, *Arch. Neurol. & Psychiat.* **8**:412-429 (Oct.) 1922.

19. Basso³ reported a case in 1922, the year in which Woltman's paper appeared. In Basso's case the clinical diagnosis (from a cervical biopsy) was Hodgkin's disease, but at necropsy there was an infiltration of the cerebral dura mater with formation of nodules. Histologically, the disease was proved to be lymphosarcoma. As to the situation of Hodgkin's disease, the literature is replete with reports of invasion of the intracranial and intraspinal dura mater. This is shown in the recent summary of the literature by K. O. Von Hagen (Lymphogranuloma [Hodgkin's Disease] with Involvement of the Spinal Cord, *Bull. Los Angeles Neurol. Soc.* **2**:20-25 [March] 1937).

20. Vernet, M.: Sur le syndrome des quatre dernières paires crâniennes, d'après une observation personnelle chez un blessé de guerre, *Bull. et mém. Soc. méd. d. hôp. de Paris* **40**:210-223, 1916.

posterior retroparotid space [Villaret²³], and dissociated forms of the posterior syndrome as reported by Avellis²⁴ [tenth nerve], Schmidt²⁵ [eleventh nerve], Jackson²⁶ [tenth, eleventh and twelfth nerves] and Tapia²⁷ [tenth and twelfth nerves]). Other cranial nerves may also be attacked and give rise to symptoms of irritative or paralytic nature, but such lesions occur less frequently than those affecting the last four cranial nerves and they are more common in the second group than in the first.

As to the second group, the French and Italian neurologists and otolaryngologists have shown a great interest in this problem and have directed attention to tumors whose origin is "peritubal" (eustachian). Jacod has stressed that intracranial extension of such tumors invariably occurs and produces neurologic symptoms because the fascial anatomic relations of this region with the base of the skull are different from those of any other region, allowing spread of the neoplasm upward to the petrosphenoidal (anterior lacerated) space, which gives access to structures in the middle fossa. The syndrome most commonly encountered is produced by irritation or paralysis of one or all branches of the trigeminal nerve and the oculomotor nerve; however, the complete syndrome is characterized by involvement of all the cranial nerves in the middle fossa (*syndrome du carrefour pétrosphénoïdal* second, third, fourth, fifth and sixth cranial nerves).²⁸ Similar observations have been described by many others; however, it has also been demonstrated that on rare occasions a tumor arising elsewhere (other than "peritubal" or in the "cavum") may spread or metastasize into this region and produce the same syndrome as well as involve other of the cranial nerves, giving rise to motor and sensory ophthalmoplegia and to paralysis of other cranial nerves (sixth, seventh [uncommonly involved], ninth, tenth, eleventh and twelfth). This, however, is probably rare. Other symptoms are frequently due to increased intracranial pressure caused by the presence of the rapidly growing mass, and occa-

21. Collet, M.: Sur un nouveau syndrome paralytique pharyngo-laryngé par blessure de guerre (Hémiplégie glosso-laryngo-scapulo-pharyngée), *Lyon méd.* **124**:121-129, 1915.

22. Sicard, J. A.: Syndrome du carrefour condylo-déchiré postérieur (type pur de paralysie des quatre derniers nerfs crâniens), *Bull. et mém. Soc. méd. d. hôp. de Paris* **41**:317-327, 1917.

23. Villaret, cited by Wilson, S. A. K., and Bruce, A. N.: *Neurology*, Baltimore, William Wood & Company, 1940, vol. 1, p. 426.

24. Avellis, G.: Klinische Beiträge zur halbseitigen Kehlkopf lähmung, *Berl. Klin.* **40**: 1-26, 1891.

25. Schmidt, cited by Wilson, S. A. K., and Bruce, A. N.: *Neurology*, Baltimore, William Wood & Company, 1940, vol. 1, p. 426.

26. Jackson, J. H.: Paralysis of Tongue, Palate, and Vocal Cord: Treatment of Obscure Forms of Metrorrhagia, *Lancet* **1**:689-690 (April 10) 1886.

27. Tapia: Un nouveau syndrome: quelques cas d'hémiplégie du larynx et de la langue avec ou sans paralysie du sterno-cléido-mastoïdien et du trapèze, *Arch. internat. de laryng.* **22**:780-785, 1906.

28. M. Jacod (La sindrome di Silvio Negri: A propos des cancers pérîtubaires et de leur propagation endocranienne, *Riv. oto-neuro-oftal.* **12**:523-529 [July-Aug.] 1935) has reproduced an obscure article written and published in 1888 in Turin, Italy, by Silvio Negri, who apparently was the first to describe the syndrome of this region and substantiate the pathology of it (Negri, S.: La sindrome di Silvio Negri. Storia d'un tumore della base del cranio. Cenni sulla malattia del Comm. Mons. Bernardo Raineri. Reperto necroscopico, *ibid.* **12**:515-522 [July-Aug.] 1935). In Italian and French literature the syndrome has recently been described under the name of "Negri-Jacob Syndrome." This is to be differentiated from the syndrome of Gradenigo or "syndrome of the petrous apex," which involves only the fifth and sixth cranial nerves (Gradenigo, G.: Ueber die Paralyse des Nervus abducens bei Otitis, *Arch. f. Ohrenh.* **74**:149-187, 1907).

sionally there is evidence of infiltration of the brain itself, though this is rarely suspected until proved at necropsy or by surgical exploration and it appears to be rather infrequent, if not rare.²⁹

From the pathologicoanatomic standpoint, the process consists of an infiltration of the dura mater until its structure is no longer grossly recognizable and of subsequent formation of tumor nodules. Or the lesion may appear as a friable, flat subdural mass of a few millimeters' thickness, not unlike an organizing subdural hematoma, which can be stripped easily from the inner surface of the dura mater.³⁰ Occasionally there is extension of the morbid process into the arachnoid and subarachnoid space and, finally, perivascular extension into the cortex of the brain.³¹ Cranial nerves are involved in the neoplastic processes both by compression and by infiltration, with concomitant interference with their function.

The third group mentioned previously, the tumors in which the spinal cord is involved, is better known than the first and second groups and is one in which the literature is much more voluminous. Because of its individual nature and problems peculiar to it, it would not be possible or expedient to discuss the group here. Suffice it to say that the spinal dura mater is involved frequently and the cord is damaged in one of the following ways or by a combination of them: (1) compression by the presence of the space-occupying new growth, (2) interference with its vascular supply and lymphatic drainage, or (3) direct extension into it by the neoplasm. Interestingly, there are problems which are special to different regions of the spinal column.

Much has been said about intracranial extension of lymphosarcoma, but we have here presented 2 cases in which the primary lesion appears to have been within the cranial dura mater. These are undoubtedly unique, for we have been unable to find a similar report anywhere in the literature. Therefore, the question whether the tumors reported on here were primary within the cranial bones or within the dura mater is important, but it appears to be fairly well answered in case 1 by the thorough necropsy. In case 2 in which there was a lamented lack

29. It is recognized that metastatic tumors (lymphosarcoma) may invade the brain more frequently than previously had been anticipated or even disseminate through it and its cavities, since altogether too frequently the author reporting such a growth has merely stated that there was "involvement of the brain" or "involvement of the nervous system." In a recent article (Gross, P., and Votawa, G. J.: *Bilateral Symmetrical Exophthalmos Due to Retrobulbar Lymphosarcoma: Report of a Case, Radiology* 31:620-621 [Nov.] 1938) the authors dismissed the intracranial findings with the statement that the choroid plexus was the site of metastatic nodules; this is undoubtedly of uncommon occurrence, though we have several such examples of metastatic lesions in the Mayo Clinic series.

30. This was the situation in the case of a woman aged 46 years, whom we have recently had the privilege of studying. Because of a history of multiple infections in the past seven years, including an abscess in the left frontotemporal region of the scalp, her present symptoms of fever, leukocytosis and sudden onset of aphasia, delirium and right hemiparesis were interpreted as caused by an infection. A subsequent drop of both temperature and number of leukocytes with a rather rapid onset of coma was taken to indicate encapsulation of an abscess of the brain in the left frontotemporal region. A small craniotomy was therefore performed, but to our surprise we encountered a subdural mass of friable tissue about 8 by 10 cm. and 3 to 6 mm. thick. Since sufficient time has not elapsed for thorough study, we submit this brief résumé as only a possible case of primary intracranial lymphosarcoma. It clinically conforms to this group and in all probability will prove to be one.

31. In surveying the literature of Hodgkin's disease it was apparent that either the invasion of the nerve tissue secondary to its invasion of the dura mater was more common than that of lymphosarcoma or there has been a greater interest over a longer period in Hodgkin's disease than in lymphosarcoma. Possibly both factors play a role.

of study at necropsy, the question seems well answered by careful analysis of the clinical records and by the fact that so far lymphosarcoma has not been reported as primary in the skull.³²

It may be well to enumerate those incidents in this case which lend credence to the primary intracranial origin of the lesion. They are as follows: 1. The primary symptoms were signs of increased intracranial pressure (headache, vertigo, tinnitus, malaise, anorexia, diminished vision, motor weakness and numbness and paresthesias of the finger tips). 2. The lump in the frontoparietal region of the scalp appeared after the first signs of involvement of the nerve tissue were manifested. 3. There was no evidence of cervical adenopathy or enlargement or infiltration of any of the structures at the base of the skull. 4. The neoplasm was found by surgical intervention. 5. The involvement of cervical lymph nodes appeared after surgical interference with the local mass, allowing spread of the lymphosarcoma through the tissues of the scalp into the cervical nodes. 6. The disease had a long course. 7. There was no evidence of tumor elsewhere in the body. 8. The tumor was present in the vault and not in the base of the skull, where tumors of "peritubal" or of cervical lymph node origin are prone to make themselves apparent. In the first statement in the foregoing list, it is well to note that in other cases in which there were intracranial metastatic growths the first symptoms have been cervical adenopathy or primary extranodal symptoms and subsequent compression of certain cranial nerves making exit through the basilar foramina, whereas this patient's symptoms, as previously pointed out, were first of all indicative of their intracranial origin.

From the point of view of pathology one may justifiably question the dural origin of the lesion in favor of its arising primarily in the diploe of the overlying skull. Since the first patient had received a seemingly minor injury to the skull, as we have mentioned already, it is conceivable that this may have produced enough reaction to form a focus of lymphocytes in the dura mater in which the tumor could have originated later. But in the second case there was no history of trauma; although the largest portion of the tumor was in the dura mater and infiltrated the adjacent leptomeninges and brain, certainly its dural origin cannot be postulated or established so easily. The absence of lymphatics within the dura mater and the leptomeninges, now well known because of the work of Weed³³ in

32. L. F. Graver and M. M. Copeland (Lymphosarcoma in Bone, *Arch. Surg.* **28**:809-824 [May] 1934) indicated the skull as the third most common site of metastatic lymphosarcoma but did not report any such tumor as primary in the cranial bones. More recently, Parker and Jackson¹² have established primary reticulum cell sarcoma of bone as a distinct clinical entity, though it is histologically identical with the same tumor of the soft parts, but they did not find any such growth primary in the cranial bones. Szutu and Hsieh, who have recently reported on this tumor (Szutu, C., and Hsieh, C. K.: Primary Reticulum Cell Sarcoma of Bone: Report of 2 Cases with Bone Regeneration Following Roentgenotherapy, *Ann. Surg.* **115**:280-291 [Feb.] 1942), did not mention it as occurring in the skull nor have we been successful in locating any such report in any of the literature available to us as late as January 1943.

33. Weed, L. H.: Studies on Cerebro-Spinal Fluid: II. The Theories of Drainage of Cerebro-Spinal Fluid with an Analysis of the Methods of Investigation, *J. M. Research* **26**: 21-49 (Sept.) 1914; III. The Pathways of Escape from the Subarachnoid Spaces with Particular Reference to the Arachnoid Villi, *ibid.* **26**:51-91 (Sept.) 1914; IV. The Dual Source of Cerebro-Spinal Fluid, *ibid.* 93-117 (Sept.) 1914. Weed, L. H.: The Meninges, with Special Reference to the Cell Coverings of the Leptomeninges, in Penfield, W.: *Cytology and Cellular Pathology of the Nervous System*, New York, Paul B. Hoeber, Inc., 1932, vol. 2, pp. 613-634.

1914, is also against either tumor's having its origin in this structure.³⁴ However, little work has been done on the late effects (the presence of residual lymphoid elements) of trauma and infection³⁵ in the dura; consequently the dura mater remains as a possible site of origin for such a neoplastic process.

Although these cases suggest such an origin they fall far short of proving it. Hence the primary development of such tumors may more probably be in the diploe of the skull. With this in mind, a search through the records of tumors of the skull studied at the clinic was made in the hope of finding a record of a lymphosarcoma localized to this structure without metastasis or extension into the surrounding tissue. This yielded a record of a case in which operation was performed and in which there were bilateral parietal subperiosteal tumors with roentgenographic evidence of multiple areas of erosion of the skull, not unlike the changes seen secondary to an underlying meningioma (roentgenographic diagnosis). However, this patient was without clinical evidence of intracranial extension. The subperiosteal tumors were removed surgically, and the underlying eroded bone was cauterized extensively with the electrosurgical unit. The operative site and surrounding areas were subsequently exposed to roentgen therapy. It is known that for seven years there was no recurrence of the neoplasms or evidence of metastasis. The tissue appeared to be a lymphosarcoma, and review of the slides confirmed this interpretation, for it was composed of lymphocyte-like cells and others resembling reticulum cells. In fact, the latter cells tended to predominate; consequently this is probably a lymphosarcoma of the reticulum cell type or possibly of a mixed type as described by Warren and Picena.³⁶

That lymphosarcoma can and does arise in bone has been known for several years, and this case might suggest just such an origin in the cranial bones for the

34. H. Rouvière (*Anatomy of the Human Lymphatic System*, translated by M. J. Tobias, Ann Arbor, Mich., Edwards Brothers, Inc., 1938, pp. 238-239) expressed the opinion that lymph crevices exist in the dura mater and communicate with adjacent channels and nodes, though he failed to state where these are or what is the nature of the "lymph crevices." Moreover, he did not state his authority for these statements, not even his own investigations. However, in substantiating his statement on the presence of pial perivascular lymph vessels he quoted the obsolete reports of the last century and before, such as those of Mascagni in 1787 and Fohman in 1838. C. K. Drinker and J. M. Yoffey (*Lymphatics, Lymph, and Lymphoid Tissues*, Cambridge, Mass., Harvard University Press, 1941, p. 7) in 1941 noted the presence of lymphatics leading from the cranium but did not mention any afferents to these. Possibly these as well as the basilar foramina are channels for the extension into the intracranial structures from cervical lymphosarcoma, as has been noted by C. Jemmi (*Su di un interessante caso di linfosarcoma peritubarico con diffusione intracranica*. *Riv. oto-neuro-oftal.* **15**:336-348 [July-Aug.] 1938), L. de Lisi (*Complicazioni nervose del linfosarcoma: necrosi midollare acuta; invasione endocranica bilaterale, sindrome della fossa petro-sfenoidale*, *Riv. oto-neuro-oftal.* **12**:209-238 [March-April] 1935), H. R. Viets and F. T. Hunter (*Lymphoblastomatous Involvement of the Nervous System*, *Arch. Neurol. & Psychiat.* **29**:1246-1261 [June] 1933), D. Paulian, I. Bistriceanu and M. Cardas (*Sarcome lymphoblastique médiastinal avec métastases ganglionnaires et encéphalo-craniennes*, *Arch. de neurol.* **3**:268-274, 1929), Woltman¹⁸ and Davison and Michaels,¹⁷ among others.

35. In this connection it is of interest to surmise the possible role of infection as a predisposing cause of lymphosarcoma. In our first case the patient did have a small active lesion of pulmonary tuberculosis which would have been difficult to diagnose clinically, but there was no evidence of tuberculosis elsewhere in the body. In another case (footnote 30) the patient whom we have recently studied had had many infections, one of which was an abscess in the left frontotemporal region of the scalp. Lymphosarcoma later developed immediately beneath this area in the dura mater. Just what relation exists between these lesions may be difficult to prove, but it does seem possible that the one predisposed to the other.

36. Warren, S., and Picena, J. P.: *Reticulum Cell Sarcoma of Lymph Nodes*, *Am. J. Path.* **17**:385-393 (May) 1941.

lesions in the 2 cases we have reported herein. But wherever the origin may have been, these interesting cases emphasize our ignorance of this group of tumors and the need for investigation of their possible origin in nonlymphatic structures as well as in the cranial bones.

SUMMARY

We have described what appear to have been 2 primary lymphosarcomas of the intracranial dura mater, the one occurring in a man and the other in a woman, aged 24 and 57 years, respectively. A third case, mentioned briefly, is possibly an instance of this type of tumor, but to date we have only surgical confirmation of the growth's belonging to this group.

The problems of the origin of these tumors either in the dura mater over the dorsolateral surface of the brain or in its contiguous overlying cranial bone have been discussed. It was admitted that the latter as the primary site of origin could not be ruled out; the tumors may well have arisen in the bony diploe of the skull.

The usual sites of origin of lymphosarcoma in the head (extracranial) have been reviewed, including the various modes of intracranial extension and the several syndromes thereby provoked (Jacod-Negri syndrome, syndromes of the last four cranial nerves, of the superior cervical sympathetic nerves, and so forth). These were contrasted with the symptoms described in 2 cases reported here.

Mayo Clinic.

EFFECT OF DIVISION OF THE SPHINCTER OF ODDI ON THE BILE DIASTASE OF THE DOG

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The observations of Opie¹ and others have established that in about 25 per cent of normal persons the ends of the common bile and main pancreatic ducts join at or before the papilla of Vater, resulting in a confluence of the secretions of these two ducts, the "common channel." Thus the anatomic arrangement is such that a calculus at the outlet, a spasm of the sphincter of Oddi or edema of the duodenal mucosa may cause reflux of the secretion from one into the other duct. That reflux of bile into the pancreatic duct may be an important factor in the causation of acute pancreatitis in some cases seems well established.

More recently considerable evidence has accumulated to indicate that the flow may be reversed, i. e., that there can be a reflux of pancreatic juice into the biliary tract.² The strongest evidence that this occurs has been based on the appearance of diastase in the bile of patients whose common bile ducts have been drained.³ Normally, hepatic bile is almost devoid of diastase.⁴ Bile from the gallbladder likewise contains no diastase or only minute amounts, considerably less than that contained in the blood.⁵ The appearance of appreciable amounts of diastase in the bile of patients who have undergone surgical operations⁶ indicates that pan-

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3. (a) Probstein, J. G.; Heifetz, C. J., and Gray, S. H.: Diastase in Human Bile, to be published. (b) Colp and Doubilet.^{2g, h}

4. (a) Gray, S. H.; Probstein, J. G., and Heifetz, C. J.: Clinical Studies on Blood Diastase: I. Low Blood Diastase as an Index of Impaired Hepatic Function, *Arch. Int. Med.* **67**:805 (April) 1941. (b) Popper.^{2d}

5. Colp and Doubilet.^{2g} Gray, Probstein and Heifetz.^{4a}

6. Popper.^{2d} Colp and Doubilet.^{2g}

creatic juice has in some manner entered the biliary tract. In the human being the common channel has been held responsible for this occurrence, and the confluence has been proved roentgenologically.^{2b} It is not possible to state at this time whether regurgitation of duodenal contents (containing pancreatic juice) through a relaxed sphincter of Oddi can or does occur. But the following experiments seem to indicate that division of the sphincter of Oddi in dogs will permit regurgitation of duodenal contents into the biliary tree. The existence of a common channel in the dog has never been demonstrated.

METHODS

Normal, apparently healthy dogs were employed in two series of experiments. In the first, 3 dogs were used to ascertain normal bile diastase values. The animals were anesthetized with pentobarbital sodium, 0.5 cc. of a 6.7 per cent solution being given intravenously for each kilogram of body weight.⁷ The abdomen was entered through a high midline incision, and the gallbladder and bile ducts exposed with as little trauma to the surrounding structures as possible. A fine aspirating needle was inserted through an avascular area in the wall of the fundus and 5 to 10 cc. of bile was removed. The common bile duct was exposed close to the junction with the duodenum and divided between clamps, and each end was ligated with silk. A small intercostal incision on the right side was then made between the two lowermost ribs, overlying the fundus of the gallbladder. It was sometimes necessary partly to free the gallbladder from the bed of the liver to effect delivery of the gallbladder through this incision. The wall was sutured to the edges of the skin with fine interrupted silk sutures, the portion of the organ previously used for aspiration being allowed to protrude about 1 cm. above the skin. A purse-string silk suture was then applied around the protruding serosa, a flanged straight metal cannula with an opening 4 mm. in diameter introduced through an appropriate-sized incision and the purse-string closed, so as to invert the edges of the incision in the gallbladder. Sometimes it was necessary to apply a second inverting purse-string suture. The length of the cannula depended on the thickness of the walls of the abdomen and the gallbladder and on its direction through these layers, but the average length was 4 cm., about 8 mm. of which was permitted to protrude beyond the skin. The cannula was flushed out with saline solution to remove blood clots, and the abdominal wall was closed in layers snugly around the cannula. By this method a steady flow of hepatic bile was secured, and the possibility of regurgitation from the pancreatic duct or the duodenum was precluded. Specimens consisting of 4 to 6 cc. of bile were collected daily for determinations of diastase, the remainder being discarded.

The common ducts of the dogs in the second series were not severed. Instead, the opening of the common bile duct into the duodenum was exposed transduodenally. This opening could usually be located without difficulty on a small mucosal papilla. When probed the duct was found to traverse the duodenal wall at an acute angle with the long axial plane of the mucosa, forming between the two lumens a musculomucosal flap which contained fibers of the sphincter of Oddi. With one blade of a thin scissors inserted in the common bile duct and the other placed on the duodenal mucosa, this flap was cut for a distance of nearly 1 cm. A wide channel between the duodenum and the common bile duct was thereby created. The duodenum was then flushed out with saline solution and closed with two layers of fine intestinal sutures. The gallbladder was cannulized in the manner described, and the external opening of the cannula stoppered. By removal of the stopper specimens consisting of 3 to 6 cc. of bile were collected by gravity flow. It was found that the bile could be collected faster after the animals were fed. The otherwise normal flow of bile into the intestine permitted the maintenance of adequate nutrition.

Several dogs subjected to this procedure were killed at the conclusion of the experiment and examined for patency of the choledochoduodenal communication. In all cases the operative wound had healed well and the opening was practically as wide as when first made.

After perfection of the technic it was possible to collect bile samples minimally contaminated by blood or by tissue juices. The appearance of blood in a bile sample necessitated its rejection, for the blood of a dog contains large amounts of diastase (about ten times that contained in human blood).

7. All types of anesthesia except that induced with chloroform exert no effect on blood diastase values and hence probably do not affect the amount of diastase in the bile (Probstein, Heifetz and Gray^{2a}).

Determinations of diastase were performed by the Somogyi technic for diastase activity of the blood⁸ modified by him for determinations of diastase activity of the bile as follows:

1. The bile is neutralized to phenolsulfonphthalein by addition of some powdered buffer mixture with a p_H of 7.⁹

2. Five cubic centimeters of the starch paste⁸ and 1 cc. of a 1 per cent solution of sodium chloride are mixed in a test tube. The mixture is placed in a water bath at 40 C. for a few minutes and allowed to reach that temperature.

3. One cubic centimeter of the neutralized bile is added, and the mixture is incubated at 40 C. for thirty minutes.

4. One cubic centimeter of 5 per cent zinc sulfate solution is added to the mixture, and after agitation 1 cc. of 0.3 normal barium hydroxide solution¹⁰ is added to precipitate the proteins. The contents are mixed and centrifuged for about five minutes. This step is to be performed without delay, because precipitation does not completely stop the diastatic activity.

5. After centrifugation the supernatant fluid is filtered, and a drop of phenolsulfonphthalein solution is added to the filtrate. Crystals of powdered sodium carbonate are then added until the indicator shows an alkaline reaction.

6. If the liquid appears turbid, it is centrifuged and filtered again.

7. The sugar is determined in this filtrate with the high alkalinity copper reagent.¹¹ Five cubic centimeters of the filtrate and 5 cc. of the reagent are used, and the mixture is heated in a water bath for twenty minutes.

8. To determine the original reducing power of the bile 1 cc. of bile is added to 6 cc. of water and precipitated with 2 cc. of 5 per cent zinc sulfate solution and 1 cc. of 0.3 normal barium hydroxide solution. From then on the mixture is treated as the bile-starch-saline solution mixture.

9. The reducing power of the bile in terms of dextrose expressed in milligrams per hundred cubic centimeters is subtracted from the value obtained for the sugar content of the incubated bile-starch-saline solution mixture.

10. If the values for diastase activity are exceedingly high, as often happens when one is working with dogs, the determination should be repeated with bile diluted 1:5 or 1:10 with water.

RESULTS

The values for diastase activity of the bile obtained from the 3 control dogs are compiled in table 1. The almost negligible amounts of diastase present are comparable to those in human beings. Measurable amounts were found for the first two or three days after the operation, which perhaps indicates admixture with minute amounts of blood or tissue juices. The results of tests on bile specimens taken from dog 2 before and after feeding indicate that ingestion of food has no effect on the diastase values, a result similar to the lack of effect of food on animal and human blood diastase.¹²

Table 2 shows the values for diastase activity of the bile of the dogs subjected to division of the sphincter of Oddi. In 5 dogs (4, 6, 11, 13 and 16) technical mishaps or death of the animal prevented obtaining bile samples after the initial gallbladder aspiration samples were secured. In the remaining dogs from the first postoperative day there was a great increase in the diastase content of the

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TABLE 1.—*Values for Diastase Activity in Cannulated Bile from the Gallbladder of Dogs Whose Common Bile Duct Was Divided*

Postoperative Day	Dog 1, Before Feeding	Dog 2		Dog 3, Before Feeding	Average Before Feeding
		Before Feeding	After Feeding		
0.....	0	0	..	0	0
1.....	23	140	109	34	66
2.....	10	32	40	18	20
3.....	0	0	20	0	0
4.....	0	0	0	0	0
5.....	..	40	30	0	20
6.....	..	40	0	..	40
7.....	0	0
8.....	0	0
9.....	123	123
10.....	0	0
11.....	0	0	0
12.....
13.....	0	0
14.....
15.....	0	0
16.....	0	0	0	..	0
17.....	0	0
18.....
19.....	..	0	0
20.....	0	0
21.....	..	0	0

TABLE 2.—*Values for Diastase Activity in Cannulated Bile from the Gallbladder of Dogs Whose Sphincter of Oddi Was Divided*

Postoperative Day	Dog 4	Dog 5	Dog 6	Dog 7	Dog 8	Dog 9	Dog 10	Dog 11	Dog 12	Dog 13	Dog 14	Dog 15	Dog 16
0.....	0	0	0	102	0	0	0	35	0	0	235	0	0
1.....	..	893	..	536	..	138	922	..	423	893	..
2.....	623	238	298	1,014	..	379	..	1,800
3.....	1,011	932	653	..	690	155	..
4.....	1,032	932	..	1,081	140	..
5.....	898	710	749	725	..
6.....	383	608	430
7.....	444	543	520	..
8.....	0	..	251	740	..
9.....	202	724	330	180	..
10.....	597	..	860	830	..
11.....	304	730	656	..	945	930	..
12.....	308	..	880	..	143
13.....	1,423	756	893	..
14.....	423	898	0	..	238
15.....	655	1,235	..
16.....	623	645	..	683
17.....	436	1,460	..
18.....	932
19.....	475	..	943
20.....	108	84	1,032	830	..
21.....	475	..	510	520
22.....	446	562	485
23.....	490	554	..
24.....	248	..	240
25.....	243	..	740
26.....	220	..
27.....
28.....	0	..	666
29.....	589	635	..
30.....	1,380
31.....
32.....	554	435	..
33.....
34.....
35.....	220
36.....	1,290
37.....
38.....
39.....	795

cannulated bile. This increase was maintained with few exceptions at a relatively constant level for a period as long as the experiments lasted, up to thirty-eight days. The sudden disappearance of diastase from the bile in an occasional sample is somewhat difficult to explain. It is likely that a temporary blockage to the reflux of duodenal contents may have resulted from a plug of mucus or a particle of solid food. A notable and not anticipated observation was that there was so little variability in the diastase content from day to day.

COMMENT

It can be concluded from these experiments that normally the hepatic or gallbladder bile of the dog contains no diastase or negligible amounts of it. It is also evident that when the sphincter of Oddi is divided, assuming *a priori* that the diastase comes from the duodenal juice, there is a reflux of duodenal contents into the biliary tree. Furthermore, at least when the cannula is inserted, some of the contents rise as high as the gallbladder. Whether the contents would reach this level had not the gallbladder been decompressed by the insertion of the cannula cannot be answered from these experiments. Furthermore, it has not been proved that a similar reflux can occur without division of the sphincter of Oddi. Such experiments, however, are quite feasible. Our experiments likewise throw little light on the occurrence of this reflux in the human being; nor has the opportunity to perform the needed experiments for verifying this assumption presented itself. That spasm of the sphincter of Oddi does occur has been adequately demonstrated. It is almost axiomatic that if muscular spasm occurs, its opposite, muscular relaxation, must also sometimes be present. Whether this relaxation is sufficient to permit reflux of duodenal contents into the biliary tract is yet unanswered. If it does occur, a potential etiologic factor of disease of the biliary tract is apparent.

It has been suggested that in some cases acute cholecystitis may have as an etiologic factor the reflux of pancreatic juice into the gallbladder.¹³ This evidence also rests largely on the finding at operation of appreciable amounts of diastase in bile from the gallbladder of these patients. Unfortunately any effect of the prolonged reflux of duodenal contents into the gallbladders of our dogs might be obscured by the irritative effects of the cannula. It was noted at autopsy, for instance, that the gallbladders of these animals were thickened and scarred and so contracted as to envelop the cannula closely. It could hardly be concluded from this that the reflux of bile was totally responsible for the pathologic change.

CONCLUSION

When the sphincter of Oddi is divided and a cannula inserted into the gallbladder of the dog, there results a reflux of duodenal contents into the common bile duct and gallbladder as measured by the appearance of diastase in the cannulated bile.

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UNUSUAL CASES OF HYPERINSULINISM AND HYPOGLYCEMIA

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I. EXTRAPANCREATIC ISLET ADENOMA AS A CAUSE OF HYPERINSULINISM AND HYPOGLYCEMIA

Masses of aberrant pancreatic tissue varying greatly in size have been described by many authors since Klob's¹ first report in 1859. Faust and Mudgett² in 1940 recorded the locations of such aberrant tissue in 370 published cases (table) as follows:

No. of Cases		No. of Cases	
Stomach	95	Diverticulum (not located)	1
Duodenum	105	Umbilical fistula	1
Duodenojejunal angle	2	Mesentery	3
Jejunum	65	Omentum	4
Ileum	18	Splenic capsule	3
Small intestine	6	Spleen	1
Diverticulum of stomach	3	Gallbladder	3
Diverticulum of duodenum	7	Cystic duct	1
Diverticulum of jejunum	1	Gastrocolic ligament	1
Diverticulum of ileum	8	Transverse mesocolon	1
Diverticulum of small intestine	2	Location questionable	18
Meckel's diverticulum	21		
			<hr/> 370

Exceedingly variable symptoms are attributable to aberrant pancreatic tissue. These symptoms may be indistinguishable from those due to simple ulcer, such as anorexia, nausea, vomiting, epigastric pain, insomnia and loss of weight. Symptoms not unlike those due to appendicitis, cholecystitis or diverticulitis have been described in association with or directly attributable to this extrapancreatic tissue. Symptoms of obstruction due to intussusception have been precipitated by abnormally placed pancreatic tissue within the lumen of the bowel. Insidiously progressive digestive disturbances together with debility and loss of weight have suggested the presence of cancer of some intra-abdominal organ.

In the reports of the cases recorded in the tabulation no mention is made of the symptoms of hyperinsulinism associated with aberrant pancreatic tissue. However, in October 1941 Rudd and Walton³ reported the case of a young man, of 29, with an extrapancreatic islet adenoma half an inch (1.3 cm.) in diameter located in the "lower part of the gastrosplenic omentum, about 1 inch (2.5 cm.) beyond

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2. Faust, D. B., and Mudgett, C. S.: *Aberrant Pancreas*, with Review of Literature and Report of a Case, *Ann. Int. Med.* **14**:717-728 (Oct.) 1940.

3. Rudd, T. N., and Walton, J.: *A Case of Islet Adenoma of the Pancreas*, *Brit. J. Surg.* **29**:266-270 (Oct.) 1941.

the lower part of the tail of the pancreas," which had been responsible for such pronounced symptoms of hyperinsulinism as epileptiform attacks, deep stupor, unconsciousness, Cheyne-Stokes respiration, drenching sweat, incontinence and rigidity of limbs, all relieved by intravenous administration of dextrose. Also experienced by this patient were morning stupor, mental confusion and loss of memory, which were relieved by a cup of sweetened tea. Slowness of speech, dulness of mentality, general weakness and muscular tremors, suggesting a parkinsonian syndrome, had also been noted. Values for blood sugar as low as 48 and 40 mg. per hundred cubic centimeters were recorded before operation. All these varied symptoms were completely relieved by the removal of the small extra-pancreatic islet tumor lying in the gastrosplenic mesentery.

In February 1942 Smith⁴ reported the case of a woman 45 years of age with a long history of a variety of complaints, including sinus infection, "dropped stomach," sick headaches, cystitis, nervousness, emotional instability, menorrhagia, anemia and pronounced general weakness and faintness relieved only by the frequent administration of food—as many as eleven meals in twenty-four hours. On one occasion a blood sugar concentration of 37 mg. per hundred cubic centimeters was recorded, associated with extreme weakness, profuse sweating and trembling, which could be relieved by eating a slice of toast. At operation for a presumed islet tumor, the pancreas was found to be normal, but on the descending portion of the duodenum just below the superior duodenal flexure there was a nodule of tissue approximately 2 by 1.5 by 0.5 cm., weighing 1.5 Gm., which microscopic examination revealed to be pancreatic tissue consisting of acini and ducts, with a few well circumscribed islets and numerous diffuse groups of islet cells. Decided improvement followed removal of the tumor, as shown by relief from the weakness, a gain in weight of 20 pounds (9 Kg.) and elimination of the necessity for frequent feedings.

In 1937 Fanta⁵ reported the case of a man aged 37 who suffered from symptoms of hypoglycemia relieved partially by the removal of a walnut-sized nodule of aberrant pancreatic tissue on the duodenum. Fanta stated that aberrant pancreatic tissue does not have the same significance with reference to hypoglycemia as does an islet adenoma.

In 1937 White and Gildea⁶ reported an instance of an adenoma of islet tissue which produced a value for fasting blood sugar of 50 mg. per hundred cubic centimeters, accompanied clinically by attacks of mental confusion, headache, dizziness and diplopia and subjectively by "thickness of the tongue." The adenoma was described as a firm, calcified nodule about 12 mm. in diameter removed from the connective tissues adjacent to the posterior surface of the head of the pancreas.

To these rarely encountered cases of extrapancreatic islet tissue producing symptoms of hyperinsulinism and hypoglycemia we add a fifth, in which the sequence of events was both interesting and instructive.

CASE 1.—On June 8, 1937, at 6 o'clock in the morning, the patient, a nurse, was first seen by Dr. Stockton at the request of her mother, who reported that she had "gone crazy." When examined at her home, the patient was sitting up in bed acutely upset mentally and unresponsive. The eyes were prominent and staring, with slight divergence of the eyeballs. The skin was

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6. White, B. V., and Gildea, E. F.: Adenoma of the Pancreas and Hyperinsulinism: Report of a Case with Studies of the Effects of Emotions, of Changes in Diet and of the Administration of Acids and of Alkali on the Symptoms of Hypoglycemia, *New England J. Med.* **217**:307-313 (Aug. 19) 1937.

pale and moist, and the pulse rate rapid, but cranial nerves, heart and lungs were normal. During examination she fell into a deep coma and was sent to the Stanford University Hospitals in an ambulance. Five minutes after arrival at the hospital, without treatment, she was

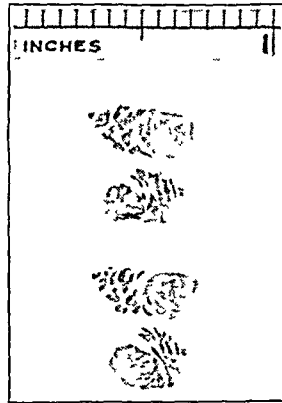


Fig. 1 (case 1).—Cross section of the tumor mounted on a glass slide (after dehydration). Note the thin capsule and the adjacent piece of lobulated pancreatic tissue removed with the tumor ($\times 1$).

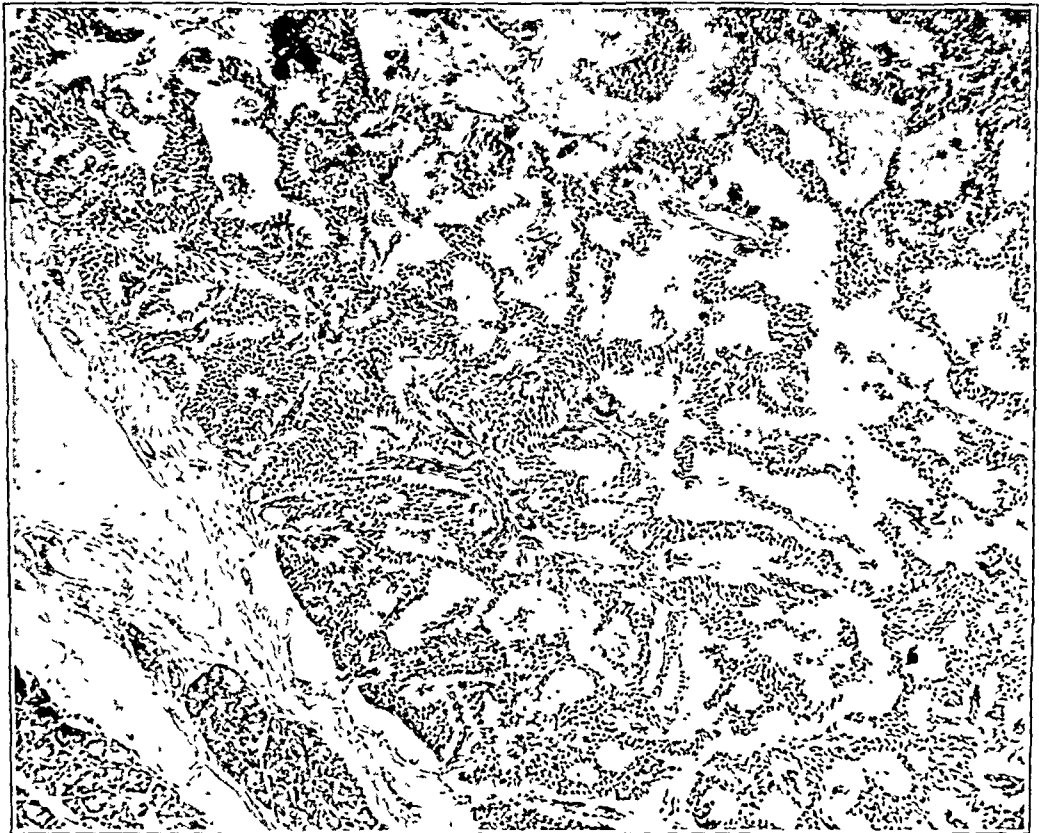


Fig. 2 (case 1).—Photomicrograph of the tumor showing the surrounding capsule and a bit of adjacent pancreas. Anastomosing narrow cords of tumor cells are separated from one another by wide vascular spaces ($\times 100$).

perfectly conscious and apparently normal, except that she felt nervous and shaky. An immediate determination of blood sugar revealed a concentration of 48 mg. per hundred cubic centimeters.

Further questioning disclosed that in the preceding six months she had had spells of dizziness and weakness, especially before breakfast and fairly regularly at 11 a. m. and 4 p. m. These symptoms were more likely to occur after she had been eating lightly or working hard. At these times she was irritable, disoriented and capable of purposeless conduct of which she had no memory.

A second determination of blood sugar (with the patient still fasting) revealed 37 mg. per hundred cubic centimeters. The red blood cells numbered 4,650,000, the hemoglobin content was 85 per cent (Sahli method) and there were 9,800 white cells, of which 94 per cent were neutrophils, 16 per cent band forms, 78 per cent segmented cells and 5 per cent lymphocytes. The sedimentation rate was 6 mm. in an hour. The urine was normal.

At operation, performed on July 19, 1937, by Dr. P. K. Gilman, a midtransverse incision permitted a thorough and complete examination of the entire pancreas. Near the extreme end of the tail, the operator found a bluish circular tumor about 0.7 cm. in diameter, which

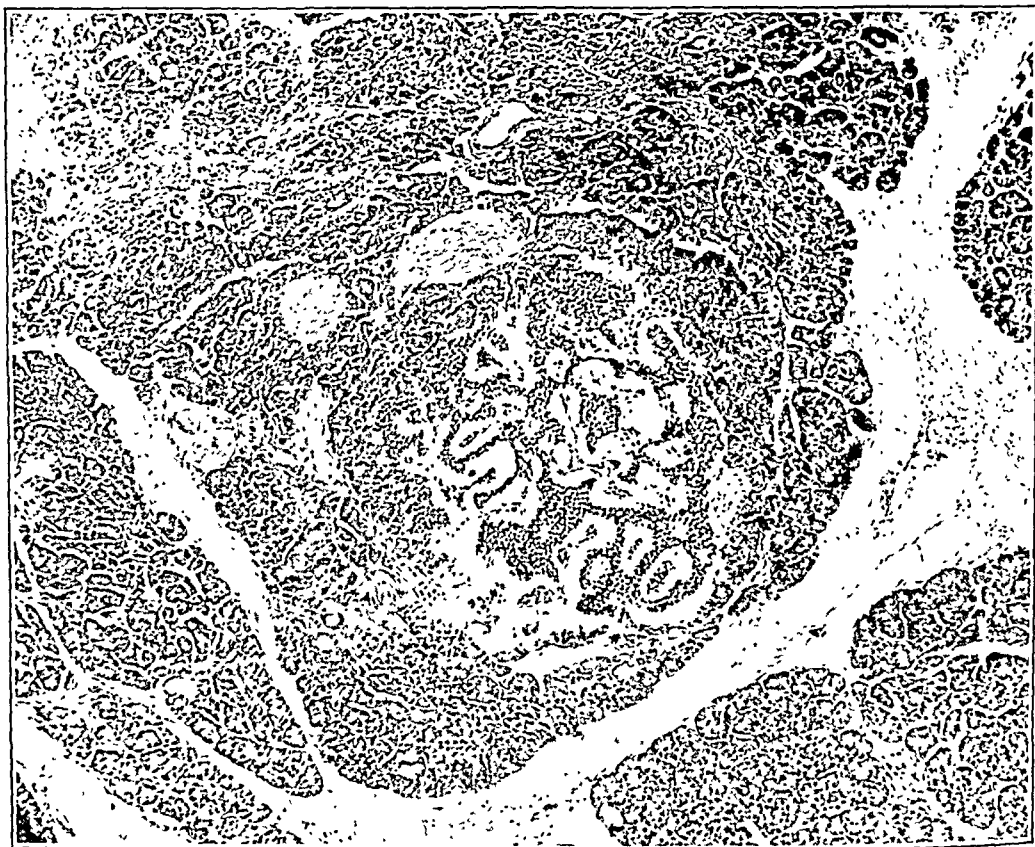


Fig. 3 (case 1).—Greatly hypertrophied islet of Langerhans in pancreatic tissue adjacent to the adenoma ($\times 100$).

was excised with normal gland about it (fig. 1). The rent in the pancreas was resutured with catgut and a gutta-percha drain introduced into this area. An uneventful recovery followed the operation, a value for fasting blood sugar of 90 mg. per hundred cubic centimeters being recorded on September 27.

Pathologist's Report.—The gross specimen consisted of a small piece of pancreas which contained a discrete purplish nodule measuring 0.8 cm. in its greatest width. Its capsule was thin. Blood freely exuded from the freshly cut surface. Situated eccentrically was a narrow rim of pancreatic tissue (fig. 1). Histologically the tumor was completely surrounded by a thin fibrous capsule. The tumor consisted of anastomosing narrow cords of polyhedral epithelial cells. These were supported on a delicate fibrous stroma which contained numerous wide blood spaces filled with blood (fig. 2). In the adjacent pancreatic tissue scattered throughout normal-appearing acinar tissue were several islets of Langerhans, some of which showed a marked degree of hyperplasia and were several times normal size (fig. 3). The diagnosis was: adenoma of the pancreas (islets of Langerhans); focal hyperplasia of the pancreas (islets of Langerhans).

It was soon apparent that she was not absolutely well. She complained frequently of an annoying tingling in her tongue and of dizziness, followed occasionally by spells of irritability and disorientation. A value for fasting blood sugar of 54 mg. per hundred cubic centimeters was recorded on May 28, 1938, and on Jan. 18, 1939, it was 56 mg. In April 1940 she again began to have spells of fainting, with loss of consciousness for brief periods, relieved by eating. About this time menstruation became scant and irregular, the symptoms from hypoglycemia being more pronounced and more frequent just before her expected periods. Dextrose tolerance tests before and after the weekly administration of estrone (theelin), in a dose yielding 10,000 international units of estrogen, revealed temporary improvement, but her difficulties continued to increase. Attacks became as frequent as two and three times daily, varying from mere tingling in the mouth to complete unconsciousness for as long as one and one-half hours, concomitant symptoms being extreme nervousness, extreme irritability, reeling and staggering gait, profuse sweating, diplopia, headaches and convulsive movements of the arms and legs. On Sept. 22, 1941, a value for fasting blood sugar of 43 mg. per hundred cubic centimeters was recorded.

It was obvious that despite the removal of one islet tumor increasingly severe symptoms of hyperinsulinism had persisted, associated with a demonstrable hypoglycemia.

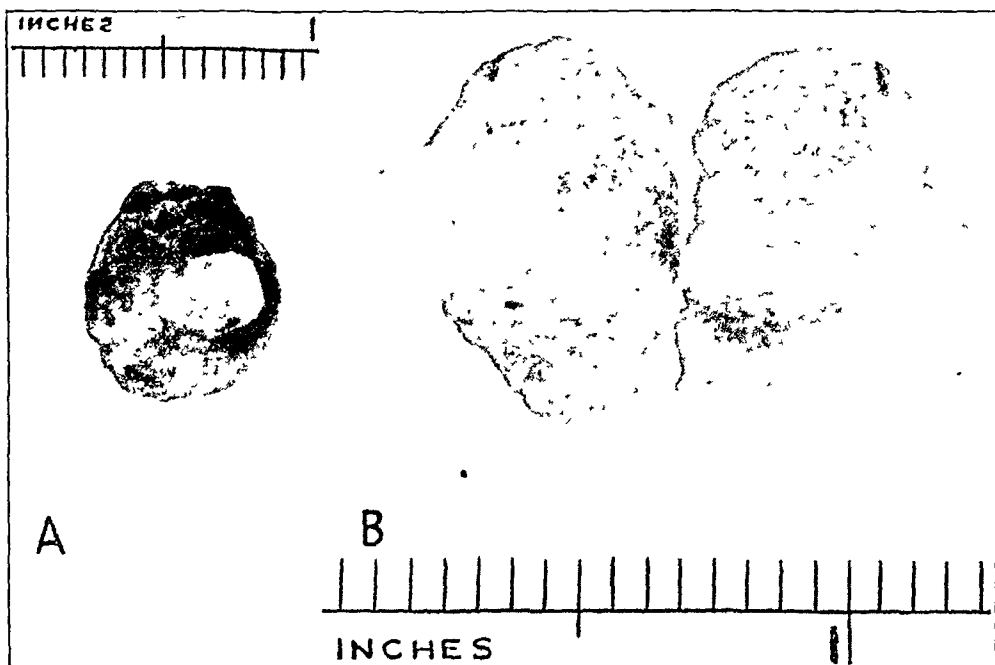


Fig. 4 (case 1).—*A*, extrapancreatic islet adenoma. Note the firm, knoblike fibrous projection ($\times 1\frac{1}{2}$). *B*, same adenoma, except that the tumor is bisected ($\times 2\frac{1}{2}$).

Reoperation was performed on Sept. 30, through the previous transverse incision. The entire pancreas was well mobilized except for the vessels along the upper border. No abnormal tissue was disclosed except for slight scarring in the part of the tail from which the first tumor was removed. However, in freeing the extreme tip of the tail, a rounded blue mass about 2 cm. in diameter was observed lying between the pancreas and the spleen. This was at first neglected, as it was interpreted as being an accessory spleen or a hemolymph node. When no other abnormality was disclosed in the pancreas, attention was again directed to this extrapancreatic mass. It was noted that instead of lying rather loosely embedded in fat and areolar tissue as accessory spleens usually are, the mass had apparently caused some fibroplastic reaction about it. It felt firmer than does a node or accessory spleen (fig. 4). Its removal by excision was therefore undertaken. Though liberally supplied with blood vessels, it was removed without difficulty, all bleeding points being controlled with transfixion ligatures of fine silk. The wound was closed without drainage.

Immediate cross section of the tumor disclosed pinkish white cellular tissue, which microscopically had the typical characteristics of islet tumor.

Postoperatively the concentration of sugar in the blood varied from 169 mg. per hundred cubic centimeters on Oct. 1, to 103 mg. on Oct. 15, 1941. At the time of writing, over a year later, the patient is perfectly well.

Pathologist's Report—The gross specimen (fig. 4) consisted of an oval, encapsulated mass 1.8 by 1.5 by 1.5 cm. Section revealed medium chocolate brown, spongy tissue. The surrounding capsule of the tumor was thin and fibrous. Projecting from one aspect was a slender, grayish white elevated nodule with a broad base. It projected for 0.6 cm. and measured 0.4 cm. in width (fig. 4A). The tumor appeared throughout to have been moderately vascular before it was cut into. Microscopically (fig. 5) the tumor was rather similar in structure to the first specimen (fig. 2). The capsule varied considerably in thickness and in places showed considerable hyalinization. Contained within the capsule were several small islets of tumor similar to that seen in the main mass. The tumor was composed of anastomosing columns of polygonal epithelial cells of medium size. All were markedly uniform in staining characteristics. Mitotic figures were absent. The tumor appeared benign, and the diagnosis was adenoma of the islets of Langerhans, extrapancreatic; heterotopy (aberrant pancreatic tissue).

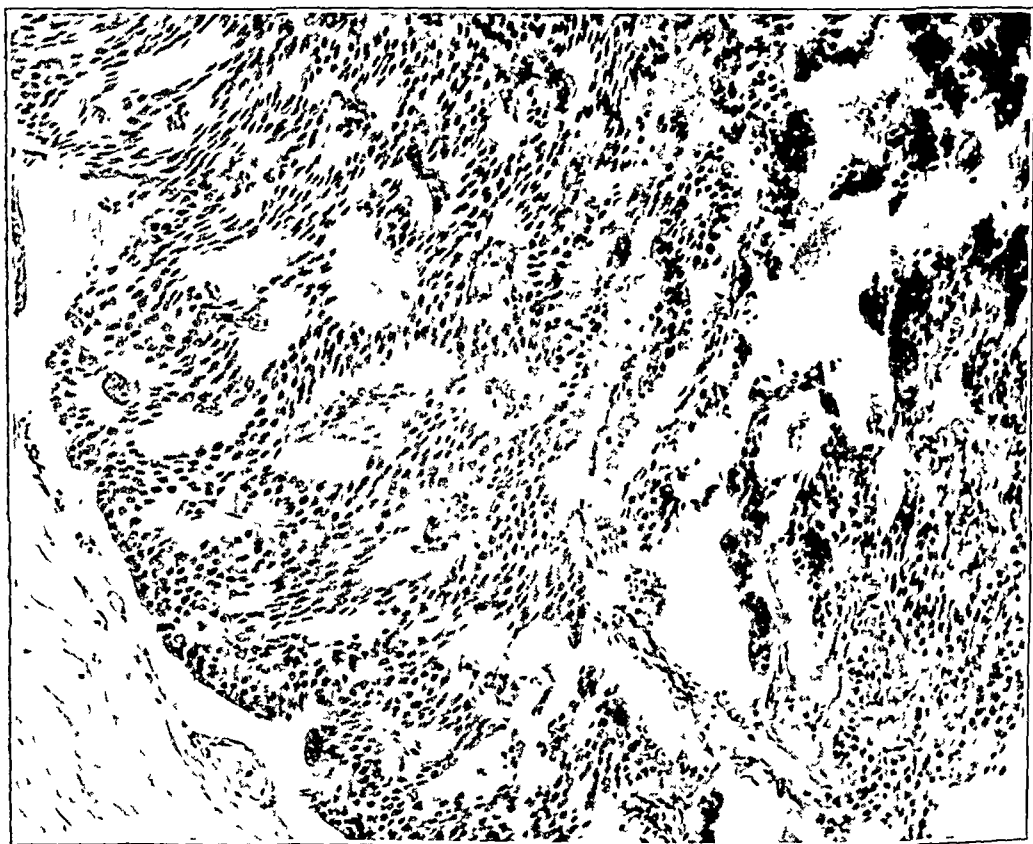


Fig. 5 (case 1).—Photomicrograph of an extrapancreatic islet adenoma. Note the similarity in structure to the pancreatic adenoma in figure 2 ($\times 100$).

COMMENT

The lessons to be drawn from this case are obvious:

1. The presence of one islet tumor does not exclude the existence of a second. In Whipple's⁷ résumé of cases of hypoglycemia to Nov. 1, 1941, multiple tumors were found in 9 of 105 cases of proved tumors of islet tissue. In 7 cases the multiple tumors were found at operation, and in 2 they were discovered at autopsy. Kalbfleisch⁸ reported a case in which one adenoma was removed at operation but at necropsy two days later four other islet adenomas were uncovered. It is

7. Whipple, A. O.: Present Day Surgery of the Pancreas, *New England J. Med.* **226**: 513-526 (March 26) 1942.

8. Kalbfleisch, H. H.: Adenome inkretorischer Drüsen bei Hypoglykämie, *Frankfurt Ztschr. f. Path.* **50**:462-477, 1937.

apparent that at operation for hyperinsulinism one cannot be entirely content with finding only one islet tumor; the entire pancreas must be exposed and searched for possible multiple islet tumors.⁹ It is further apparent that even though one tumor is found within the pancreas, a careful search for a tumor outside the pancreas must be made as well, and that suspicious bluish firm nodules should be removed.

2. Hypoglycemia may be due to an islet tumor that lies wholly outside a perfectly normal-appearing pancreas. For patients who have been proved to have hypoglycemia and who exhibit Whipple's "essential triad: attacks of central-nervous-system disorder—motor, vasomotor or psychic—coming on during the fasting state; fasting blood-sugar levels of 50 mg. per cent or less; and immediate recovery from these attacks on the administration of glucose by mouth or by vein," failure to find an intrapancreatic tumor after complete and thorough search of the entire pancreas should be followed by a wide search for abnormal masses in the localities where extrapancreatic tissue is most frequently found, according to the table provided by Faust and Mudgett.

Pertinent to this discussion are the cases reviewed by David¹⁰ in which partial or subtotal pancreatectomy was performed for hypoglycemia because no intrapancreatic islet tumor was demonstrable. In the cases in which less than half of the pancreas was removed, only 3 of the 14 patients who survived were improved. This was interpreted as emphasizing the need of a subtotal rather than partial resection of the pancreas in those cases in which no islet tumor can be found. It should be noted, however, that failure to obtain the desired effect after partial pancreatectomy in cases of hyperinsulinism characterized by the essential triad may more likely be due to failure to find the adenoma either in the remaining pancreas itself or in extrapancreatic tissues. The latter possibility may explain the following puzzling experience:

In 1928 Holman and Railsback¹¹ reported the removal of about two fifths of the pancreas from a patient with hypoglycemia without permanent benefit. Because of difficulties encountered in controlling bleeding from branches of the splenic artery and vein, it was suggested by Holman and Railsback that a splenectomy would facilitate pancreatectomy, a procedure which has since been adopted (Thomason¹²). Subsequently this same patient was operated on twice at the Mayo Clinic¹³ for persistent hypoglycemia, first by Dr. E. Starr Judd and on a second occasion by Dr. Waltman Walters. At the third operation practically all the remaining identifiable pancreatic tissue was removed without apparent benefit to the hypoglycemia. Inasmuch as this patient, both preoperatively and postopera-

9. The outcome in case 1, as well as in some of the cases previously referred to, indicates that occasionally there exists a definite "islet imbalance." In some cases this is suggested by the presence of multiple tumors. In case 1 it was produced by the development of a second tumor and by the existence of hyperplastic islets in the resected pancreatic tissue (fig. 3). This might indicate that the islet disturbance is a hyperplastic functional response secondary to other factors. If such a hypothesis is tenable, one would expect such a factor to maintain its effectiveness and to lead, most probably, to further local adenomatous hyperplasia of the islets and even to formation of a true adenoma.

10. David, V. C.: Indications and Results of Pancreatectomy for Hypoglycemia, *Surgery* 8:212-224 (Aug.) 1940.

11. Holman, E., and Railsback, O. C.: Partial Pancreatectomy in Chronic Spontaneous Hypoglycemia, with Review of Cases of Hypoglycemia Surgically Treated, *Surg., Gynec. & Obst.* 56:591-600 (March) 1933.

12. Thomason, G.: Hyperinsulinism, Hypoglycemia, Subtotal Pancreatectomy, *West. J. Surg.* 43:185-192 (April) 1935.

13. Carlson, L. A., and Ryncarson, E. H.: An Unusual Case of Spontaneous Hypoglycemia, *Proc. Staff Meet., Mayo Clin.* 12:486-490 (Aug. 4) 1937.

tively, had all of Whipple's essential triad of symptoms, the assumption is justified that he still has an islet tumor hidden away in some location where extrapancreatic tissue is occasionally found.

II. EXTRAPANCREATIC ISLET ADENOMA NOT ACCOMPANIED BY FUNCTIONAL DISTURBANCE

It is well recognized that not all hyperplasias of endocrine glandular tissues are accompanied by functional disturbance. Some adenomas, even though they morphologically mimic rather closely the structures from which they arise, are not sufficiently differentiated physiologically to assume the functions of their



Fig. 6 (case 2).—Adenoma containing aberrant islets of Langerhans in the wall of the duodenum. Note the narrow anastomosing delicate cords of cells supported by delicate fibrous stroma which also supports sinusoidal vascular spaces ($\times 50$).

prototype cells, namely, the manufacture of specific hormones. This is well recognized, for example, in adenomatous hyperplasias of the hypophysis, cortical tumors of the adrenal and Leydig cell tumors of the testis, as well as in granulosa cell and theca cell tumors of the ovary. Therefore, it is not surprising that one should occasionally encounter heterotopic islet tissue which does not cause hyperinsulinism.

The following case illustrates this point:

CASE 2.—Mrs. M. L., 61 years of age, entered the French Hospital in obvious shock, suffering from generalized peritonitis which had developed secondary to perforation of a diverticulum of the sigmoid colon. Her past history was irrelevant. At autopsy, aside from an acute peritonitis with 1,300 cc. of foul, seropurulent exudate, a cortical adenoma of each adrenal and an adenoma in the wall of the proximal portion of the duodenum were found. The

left adrenal contained an adenoma 0.8 cm. in width, and the right, one whose diameter was 1.0 cm. Situated in the anterior wall of the duodenum, 2.0 cm. distal to the pylorus, was a small grayish yellow submucosal nodule 0.4 cm. in width. Histologically the duodenal nodule possessed the typical structure of an islet adenoma (fig. 6).

In this case neither the heterotopic islet tissue in the duodenum nor the adrenal cortical adenomas were associated with detected physiologic disturbances.

III. CARCINOMA OF ISLETS OF LANGERHANS DEVELOPING PRESUMABLY ON THE BASIS OF AN OLD CALCIFIED ADENOMA

Most of the adenomas and carcinomas of pancreatic islet tissue have been rather small, the majority being under 2 cm. in width, and have been characterized by a rather short duration of symptoms prior to discovery. The case about to be presented is unusual and is being reported for several reasons. Prodromal symptoms existed fourteen years before the development of symptoms directly referable to hyperinsulinism. The prodromal period was followed by a two year period in which there was a rather rapid progression of the symptoms. At autopsy, a tumor 12 cm. in width containing a centrally calcified area 3.5 cm. in width was found in the tail of the pancreas. It is probable that the calcified portion represented a long-standing adenoma productive of only small amounts of insulin, thus accounting for the indefinite symptoms of the first fourteen years. It is also probable that coincidentally with the carcinomatous change in the adenoma the output of insulin increased; this would account for the appearance of symptoms clinically attributable to hyperinsulinism and the rather rapid progression of symptoms during the last two years of life. There were innumerable metastatic tumors in the liver and all of them uniformly showed a striking resemblance in structure to normal islet tissue.

CASE 3.—P. C., a man 45 years of age, entered the French Hospital on June 18, 1933 and again on August 25. He died October 25.

History.—In 1917, sixteen years before his admission to the hospital, the patient began to have spells of "weakness" which would last for two to three weeks at a time and which were concurrent with the development of a sore tongue. The tongue would become red and transverse and longitudinal fissures would develop. The attacks had shown a gradual increase in severity by the end of a year, and in 1921 they were so much worse that the patient entered a hospital for a period of eleven weeks. No definite diagnosis was made, but for six years (until 1927) the patient was fairly well, except for transient weakness. The symptoms then increased in severity for two years, after which there was improvement for three years (until 1931).

In the last two years prior to the patient's admission there had been a noticeable change, characterized by a considerable increase in appetite and much greater discomfort occasioned by the spells of weakness. During these spells, which were extremely bothersome, he would become very dizzy, have blurring of vision and be unable to talk. At first the attacks were periodic, several days apart, but they became more frequent and ultimately occurred every day. (The patient had also sought outside medical care and from different physicians had received the diagnoses of "brain tumor" and "epilepsy.") After an interval the patient returned to the French Hospital and this time stated that his attacks had become as numerous as two a day, occurring before breakfast and late in the afternoon. He had discovered that by taking nourishment, such as orange juice, he could ward off an attack or obtain relief in a few minutes.

He had had the usual diseases of childhood, but no operations or accidents. He had influenza in 1918. Both parents, 3 brothers, 1 sister and 3 children were living and well. His wife had had no miscarriages or stillborn children. There was no history of gout, diabetes or cancer in the family.

Physical and Roentgen Examinations.—The patient was well developed and well nourished and weighed approximately 140 pounds (63 Kg.). The abdomen was scaphoid, and on palpation a large, tender hard mass was found in the left upper quadrant. A flat plate roentgenogram of the abdomen revealed an opaque shadow under the eleventh rib, situated in or near the tail of the pancreas.

Laboratory Studies.—Blood sugar values were as follows: on June 22, 37.5 mg. per hundred cubic centimeters, on June 27, 40.0 mg.; on July 5, 40.2 mg.; on July 11, 37.3 mg.; on August 26, 36.3 mg.; on August 28, 27.0 and 29.1 mg. before operation and 250.0 mg. during operation and after administration of 100 cc of 10 per cent dextrose solution intravenously; on October 23, 75.0 mg.

On August 2 the basal metabolic rate was +4 per cent. On September 16 the cholesterol content of the blood was 51.7 mg. per hundred cubic centimeters. A dextrose tolerance test carried out on August 28 revealed a fasting blood sugar of 27 mg. per hundred cubic centimeters. After one hour the value was 133.3 mg. per hundred cubic centimeters, and after two hours, 142.3 mg. A gastric analysis (Ewald) made on June 22 revealed a total acidity of 61 degrees and free hydrochloric acid, 36 degrees. Analysis of the stools on September 7, when the patient was on a Schmidt test diet, revealed no excess of fatty acids or soaps. The clinical diagnosis was hyperinsulinism and cyst of the tail of the pancreas.



Fig. 7 (case 3).—Pancreas showing a large tumor involving the tail and the distal half. The tumor is cut in the midsagittal plane, and half is reflected downward. Centrally, outlined by "A," are faint outlines of a calcified mass. The surrounding peripheral tissue is carcinoma of islet origin ($\times \frac{1}{2}$).

Course.—Diagnosis was established a few days after the patient's admission to the hospital, when the blood sugar value was found to be 37.5 mg. per hundred cubic centimeters. Dextrose afforded immediate relief of symptoms. Exploratory laparotomy was performed September 28. A preoperative blood sugar value was 27.1 mg. per hundred cubic centimeters (100 cc. of 10 per cent solution of dextrose was administered intravenously during the operation). A large mass was found in the tail of the pancreas. Adjacent veins were greatly distended. On the inferior surface of the liver a hard nodular mass was found. Biopsy of both the pancreatic and hepatic tumors revealed a carcinoma of islet tissue. Postoperatively the patient was given 2,000 cc. of 10 per cent solution of dextrose intravenously every day for four days. His course was uneventful until the tenth day, when after a severe coughing spell the abdominal wound opened and allowed a partial evisceration. From this time on the patient failed to respond to therapy and became progressively weaker. On the twenty-fifth postoperative day there devel-

oped signs of extreme mental confusion which did not respond to dextrose. He lapsed into a semicomatose state and died on the twenty-seventh day. The final clinical diagnosis was carcinoma of the pancreas with metastases to the liver and hyperinsulinism.

Autopsy (Performed Three and One-Half Hours After Death).—A surgical wound in the upper portion of the right rectus muscle showed healing per primam intentionem. The peritoneum was smooth and glistening except for a few tiny adhesions near the operative sites.

A large tumor the size of a fist was present at the fossa duodenalis. At this site the peritoneum had been incised for biopsy. Veins in the ligamentum gastrocolicum were large, tortuous and filled with dark antemortem thrombus. On palpation the tumor was found to occupy the tail of the pancreas and to be rather sharply circumscribed.

The head of the pancreas and the proximal third of the corpus were normal in appearance and size (fig. 7). In the proximal portion the pancreatic duct was patent, but distally in the neighborhood of the tumor it became completely occluded. Situated in the tail was a large, slightly lobulated tumor, which measured 12 by 8 by 8 cm. Its freshly cut surface revealed lobulation with coalescent peripheral satellite nodules ranging from pale gray to yellow. In the

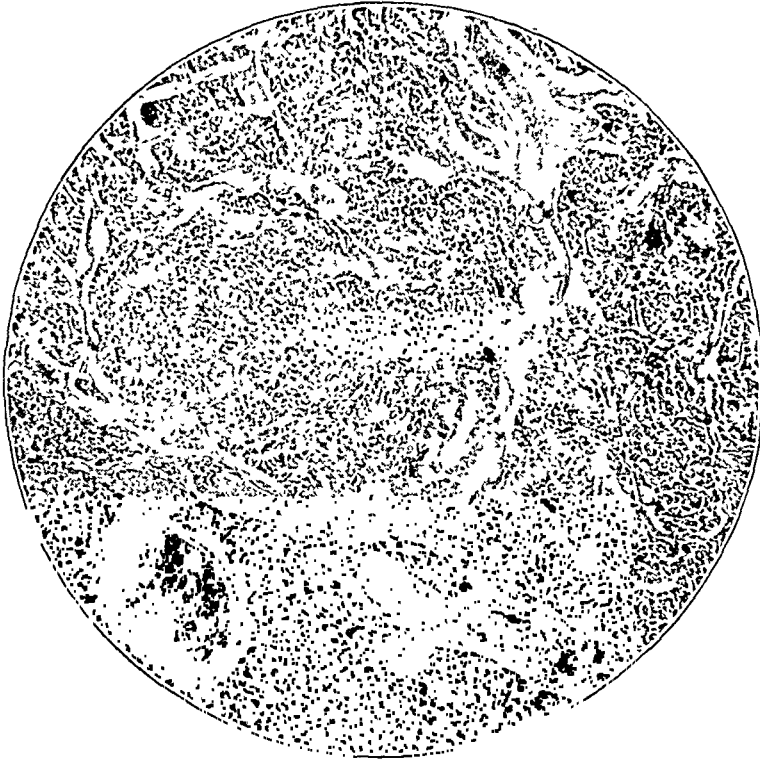


Fig. 8 (case 3).—Metastasis in the liver. Note the mimicry of islet structure by the tumor.

center was an oval area 3.5 cm. in width with slightly trabeculated stroma impregnated with calcareous material. It was fairly well circumscribed but was surrounded by tumor (fig. 7).

The liver was of medium size, measuring 27 by 21 by 8 cm. Over the convexity of the main lobe were two white nodules 4 and 5 cm. in width. Near the falciform ligament was a mass 7.5 cm. in width, and near the right coronary ligament was a mass 7 cm. in width. The smaller masses were milky white in contrast to the larger ones, which were pale yellow. On section all were found to be sharply circumscribed and to resemble closely in appearance the tumor comprising the peripheral portions of the pancreatic mass. Several smaller nodules varying from 1 to 2 cm. in diameter were scattered elsewhere throughout the parenchyma. No other metastases were found.

Both adrenals were normal in size and contained abundant cortical lipid but showed a considerable number of small nodules in the cortex.

The prostate was small, approximately two-thirds normal size. There were no foci of adenomatous hyperplasia.

Histologic Examination.—The pancreatic tumor was composed of anastomosing narrow cords of pale epithelium-like cells which were cuboidal to polygonal and of medium size. They

possessed slightly granular cytoplasm. Only a few showed hyperchromatic nuclei. Mitotic figures were extremely infrequent. A fine to moderately fibrous stroma also supported small sinusoidal vascular spaces. The resemblance of the tumor cells to those of islets of Langerhans was striking.

Section of the masses in the liver revealed tissue whose structure was essentially similar to that of the pancreatic tumor (fig. 8). The tumor was sharply demarcated from the adjoining hepatic tissue.

In the adrenal cortex there were numerous foci of adenomatous hyperplasia. Several small adenomas were contained within the adrenal capsule.

Anatomic Diagnosis.—The anatomic diagnosis was as follows: carcinoma of the islets of Langerhans; metastatic carcinoma of the liver; focal cortical hyperplasia of the adrenals; pigmentation of the skin of the hands; terminal bronchopneumonia; thrombosis of veins in the gastrocolic ligament.

IV. HYPOGLYCEMIA; APPARENTLY FUTILE EXPLORATION FOR ISLET ADENOMA; COMPLETE CURE

CASE 4.—A patient 40 years old, the mother of three children, had been troubled for two years with weakness and faintness relieved by the ingestion of sweets. In April 1937 the patient was found one morning at 7 o'clock apparently unconscious and unresponsive but was easily revived by the administration of orange juice. The next morning she was again found unconscious. The blood sugar value at this time was 33 mg. per hundred cubic centimeters. During a subsequent stay in the hospital the blood sugar values were found to lie between 40 and 60 mg. per hundred cubic centimeters with a high carbohydrate diet; between 60 and 70 mg. with a high fat diet, and between 70 and 90 mg. with a high protein diet. Further examinations disclosed a normal sella turcica, a normal gastrointestinal tract and a normal gallbladder. Pyclograms were normal, and tests of hepatic function gave normal results.

Despite an adequate and well supervised dietary regimen, the patient continued to have episodes of faintness and unconsciousness four or five times weekly. At one time her maximum period of normal comfort without food was four hours. A year later she could scarcely let two hours pass without eating. At night she found it necessary to set her alarm to be awakened every two hours for food!

On March 18, 1938, a laparotomy was performed by Holman, which revealed only normal viscera. The pancreas was separated completely from all surrounding structures except the blood vessels which entered its superior surface. All surfaces were carefully inspected and palpated for small masses, but none was discovered except a small nodule which microscopically showed chronic lymphadenitis.

Subtotal resection of the pancreas was carefully considered at the time of operation but was rejected in view of the doubtful results from such a procedure.

The patient made an uneventful recovery and has had not a single attack of unconsciousness since the operation. Although still a thin and small woman, she is eating normally and at the time of writing is driving a motor truck!

No explanation for the result can be offered. Rather apologetically it is suggested that some form of denervation was accomplished, but as the arterial supply was scarcely interrupted it is difficult to substantiate this possibility.

SUMMARY

1. Recorded in the literature are 4 cases of extrapancreatic islet adenomas producing symptoms of hyperinsulinism and hypoglycemia which were entirely controlled by removal of the extrapancreatic adenoma. To these 4 is added a fifth case in which the removal of one intrapancreatic adenoma failed to relieve the hypoglycemic symptoms, but in which the removal of a second islet adenoma in the gastrosplenic ligament produced complete cure.

In any operation undertaken in a case in which Whipple's triad of hypoglycemic symptoms is present, the possibility of multiple adenomas must be borne in mind as well as the possibility of an islet tumor lying in extrapancreatic tissue. Failure to find an intrapancreatic tumor should be followed by careful search for an islet tumor in those sites where heterotopic pancreatic tissue is frequently found.

2. Reported also is a case of heterotopic islet adenoma of the duodenum without hypoglycemic symptoms.

3. A case of islet carcinoma apparently engrafted on a calcified islet adenoma which presumably had been responsible for hypoglycemia of varying severity over a period of sixteen years is presented.

4. A bizarre case of hypoglycemia characterized by episodes of unconsciousness and blood sugar values as low as 33 mg. per hundred cubic centimeters is reported. The patient's abdomen was explored for an islet adenoma but none was found. In the course of the operation the pancreas was isolated from all surrounding structures, although its arterial supply was not interrupted. No evidences of hypoglycemia have ever again appeared. No explanation for this astonishing and unexpected result is offered.

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HEMORRHAGIC HYPOTENSION AND ITS TREATMENT BY INTRA-ARTERIAL AND INTRAVENOUS INFUSION OF BLOOD

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The suggestion was made to us by Col. Sam F. Seeley (Medical Corps, U. S. Army) that intra-arterial infusion of blood or plasma under a pressure equal to normal arterial pressure might have advantages over the conventional method of intravenous infusion in the treatment of shock. It was his view that intra-arterial infusion would elevate blood pressure rapidly, thus restoring tissue perfusion without delay; further, the exact amount of blood or plasma required to reestablish arterial pressure at any desired level would be given without the use of complex or inaccurate methods of calculation, since the intra-arterial infusion would automatically check itself at this level. This report is based on an experimental study of Colonel Seely's suggestion.

We have also sought some test indicating the effects of hemorrhage and hypotension on the vascular system. Page¹ had shown that the pressor response to angiotonin was severely depressed by hemorrhage; subsequently we found that the response to epinephrine hydrochloride is similarly depressed. Both substances were employed as indicators of the state of vascular responsiveness.

It became necessary, once uniformity of the experimental conditions had been achieved, to devise an infusion apparatus which allowed blood to be given under controlled pressure. It was also essential that blood be withdrawn from or injected into the subject without clotting and without the use of excessive amounts of anticoagulant.

The first experiments established that animals in which a standard hypotension has been produced do not recover spontaneously. In a second series of experiments dogs were treated with either intra-arterial or intravenous infusion of all the blood removed during hemorrhage and the results compared. In a third series the two methods of infusion were compared after administration of only half of the blood removed. Finally, 3 patients suffering from traumatic shock were given plasma to demonstrate the feasibility of intra-arterial infusion in the treatment of shock in human beings.

METHODS

Dogs weighing 9 to 14 Kg. were starved for twenty-four hours and then anesthetized by the intraperitoneal injection of 30 mg. per kilogram of body weight of sodium pentobarbital. If the animals were not starved, the occurrence of abdominal distention in some dogs decreased their ability to withstand prolonged hypotension because the increased pressure against the diaphragm from the stomach and intestines handicapped respiration and cardiac function. Distention was hazardous for another reason, namely, danger of vomiting and aspiration of food during the period of recovery. It did not occur when the animals were starved for twenty-four hour periods preceding the experiment.

The experiments were performed under aseptic conditions secured by autoclaving all of the apparatus except the manometer and the pressure bulb. The apparatus used for bleeding

From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital.

1. Page, I. H.: *J. Exper. Med.* **78**:41, 1943.

and for storing the blood and returning it to the dog by either the intravenous or the intra-arterial route is shown in the diagram (fig. 1). The femoral artery was dissected out and a glass cannula with a side arm (A) inserted. It was filled with heparin solution and connected to a mercury manometer (B) which recorded the arterial pressure on a kymograph. The side arm was connected by a short rubber tube to a glass Y tube. One limb (C1) was fitted with an adapter (D) which allowed a 10 cc. Luer syringe to be attached; the other limb (C2) was connected to an inverted bottle (F) which was suspended 12 inches (30.5 cm.) above the dog's hindleg. This bottle served as a reservoir for the blood which entered through the tube (E) and which could be returned to the dog through the filter (G). Air could escape from the bottle through a long glass tube (I) which extended above the surface of the blood. Pressure could be exerted on the blood within the reservoir by connecting this tube with the pressure bulb (K). The amount of pressure was recorded by the mercury manometer (J). The flow through these tubes was controlled by screw clamps (I, II and V) and by pinch clamps (III and IV). After the apparatus had been assembled the tube con-

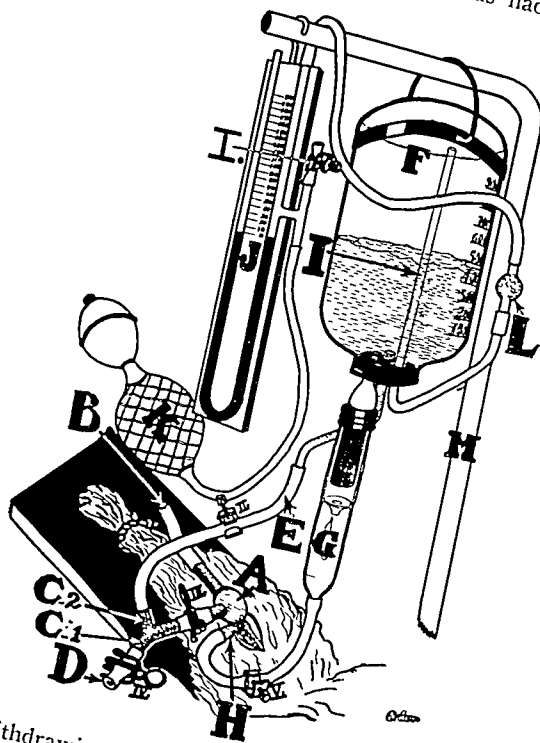


Fig. 1.—Apparatus for withdrawing blood from femoral artery and returning it either intra-arterially or intravenously. A, glass cannula with a side arm inserted in femoral artery; B, rubber tubing leading to a mercury manometer for recording arterial pressure; C1, limb of glass Y tube leading to adapter (D); C2, limb of Y tube connected by rubber tube (E) with blood reservoir (F); D, adapter for connecting 10 cc. Luer syringe; G, outlet from blood reservoir through a steel cloth filter; H, tube from blood reservoir connected to a cannula in femoral vein for venous return of blood; I, tube connected to limb C2 of glass Y tube for intra-arterial infusion; J, air inlet in blood reservoir; K, pressure bulb for recording pressure within blood reservoir during intra-arterial infusion; L, cotton filter for increasing pressure within blood reservoir; M, iron filter for supporting apparatus; N, screw clamp on tubes leading to and from blood reservoir; O, pinch clamps on side arm of cannula and limb of Y tubing leading to adapter.

Bleeding was done with this apparatus by opening clamp I on the air vent, closing clamp I' on the outflow tube of the reservoir, closing clamp II' on the limb of the Y tube and on the outflow tube of the reservoir, closing clamp III' on the limb of the Y tube and

removing clamp *III* on the side arm of the cannula. The rate of flow was controlled by adjusting clamp *II* on the tube between the glass *Y* and the reservoir. Bleeding was stopped by closing this clamp.

Ten cubic centimeters of 10 per cent solution of sodium citrate was injected through tube *E* into the reservoir before the hemorrhage was started. This was sufficient to prevent clotting of the blood removed during the initial hemorrhage. Five cubic centimeters of sodium citrate solution was then added for every 100 cc. of blood received during the course of the experiment.

Since most of the heparin solution had been carried from the arterial cannula to the reservoir during the hemorrhage, clotting occurred within the cannula unless the anticoagulant was quickly replaced after each hemorrhage. After the initial hemorrhage, heparin was injected into the arterial cannula from the Luer syringe attached to the adapter *D* by removing clamp *IV* on the limb of the *Y* tube. When sufficient anticoagulant had been injected, clamp *III* was replaced on the side arm of the cannula.

It was equally important to prevent clotting of blood in the tube leading to the reservoir from the glass *Y*. Citrated blood was withdrawn from the reservoir into the syringe attached at *D* by opening clamp *II*. This blood was drawn back and forth through this tube until it was thoroughly citrated. Five cubic centimeters of citrated blood was left in the syringe, and clamp *IV* was replaced.

Bleeding was resumed by removing clamp *III* from the side arm and adjusting clamp *II*. After each hemorrhage the 5 cc. of citrated blood which had been left in the syringe was injected into the arterial cannula as anticoagulant instead of heparin solution.

The external jugular vein was dissected out and ligated cephalad. A no. 12 French rubber catheter was inserted until the tip was approximately at the level of the atrium. It was filled with heparin solution and connected to a water manometer.

Method of Bleeding to Produce Sustained Hypotension.—Bleeding was done in stages as follows: An initial large volume of blood, equivalent to 2 per cent of the animal's body weight, was withdrawn in a period of less than three minutes. After partial recovery portions of 100 cc. each were withdrawn at intervals until the desired degree of hypotension was attained. When the arterial pressure remained at 50 mm. of mercury the volume of each hemorrhage was reduced to 50 cc. and the rate of bleeding was decreased. When the pressure reached 40 mm. of mercury the volume was reduced to 10 to 20 cc. of blood slowly withdrawn.

With some practice the arterial pressure could be brought to and kept at 30 mm. of mercury in the majority of experiments within forty to sixty minutes. In some it was necessary to withdraw 10 or 15 cc. of blood if the arterial pressure began to rise, and in other experiments if the pressure declined below 30 mm. of mercury it was necessary to reinfuse small quantities of blood. Hypotension was maintained for forty minutes before the vascular responsiveness to angiotonin or epinephrine was tested. The maximum amount of blood removed was 7.2 per cent and the minimum 3.1 per cent of the body weight, and the duration of the periods of sustained hypotension (30 to 40 mm. of mercury) varied from thirty-three to one hundred and six minutes.

CRITERIA USED TO INDICATE THE EFFECTS OF PROLONGED HYPOTENSION

Possibly because of differences in age, state of nutrition, hydration and breed among the dogs, maintenance of arterial pressure at 30 mm. of mercury for the same length of time did not always have the same effect on survival. The pressor responses to angiotonin and epinephrine were therefore used as additional criteria in estimating the effect of prolonged hypotension.

The angiotonin solution was standardized so that 0.1 cc. gave the same rise in arterial pressure in a pithed cat as 0.002 mg of epinephrine hydrochloride. In each experiment it was administered before bleeding in order to determine the amount necessary to produce a rise of at least 16 mm. of mercury. For most dogs 0.2 cc. was sufficient, but for some 0.4 cc. or even 1.0 cc. was needed.

After arterial pressure had been maintained at 30 mm. of mercury for forty minutes, the same dose of angiotonin was administered as had been given in the prehemorrhagic stage. If the response had been reduced to less than 8 mm. of mercury treatment was started, but if it had not been sufficiently diminished hypotension was continued, and the angiotonin injection was repeated at intervals of from ten to fifteen minutes.

During the course of these experiments it was found that prolonged hypotension also diminished the pressor response to 0.1 to 0.2 cc. of a 1:10,000 solution of epinephrine hydrochloride. In 4 experiments the hypertensive effects of angiotonin and epinephrine hydrochloride paralleled one another. Because of the difficulty of obtaining sufficient angiotonin, epinephrine hydrochloride was used in many of the experiments.

METHOD OF TREATMENT OF POSTHEMORRHAGIC HYPOTENSION

In those experiments in which the intra-arterial route was used, the rubber tube from the filter *G* (fig. 1) was placed on a limb of the glass *Y* tube *C1*. This permitted the blood to flow from the reservoir through the filter and into the arterial cannula in the femoral artery. Tightening clamp *I* closed the air vent, and compressing the bulb *K* raised the pressure in the reservoir to 50 mm. of mercury. Infusion began when clamps *V* and *III* were opened.

As the systemic arterial pressure increased, the rate of infusion decreased until the inflow became intermittent and then stopped altogether. When this occurred the pressure within the reservoir was raised to 80 mm. of mercury and infusion resumed. In some experiments a pressure of 120 mm. of mercury was necessary to complete the infusion. The average rate of administration of blood was 48 cc. per minute. Intravenous infusion was accomplished by connecting the tube from the filter *G* to a glass cannula in the femoral vein *H*.

In some experiments a rise of more than 5 cm. of water in venous pressure served as a sign for reducing the infusion rate. In other experiments the venous pressure was not used as a guide because experience showed that a rate of 100 and 200 drops of blood per minute was below the limit at which venous pressure rose to alarming heights.

After infusion the artery and veins were ligated, the cannulas removed and the wounds sprayed with sulfathiazole powder.

TABLE 1.—Sustained Hypotension—Not Treated

Experi- ment No.	Hematocrit Value, Mm.	Arterial Pressure Before Bleeding, Mm. Hg	Blood Removed, Cc.	Blood Removed, per Cent of Body Weight	Time for Hemor- rhage, Minutes	Arterial Pressure After Hemorrhage, Mm. Hg	Survival, Minutes	Hematocrit Value Before Death, Mm.
1	28	120	320	3.9	25	34	46	20
2	55	144	430	4.5	40	30	260	45
3	55	160	595	5.9	53	40	123	41
4	34	130	370	3.3	55	35	55	33
5	35	160	280	4.0	17	20	35	35
6	38	124	470	3.9	18	20	20	
7	46	156	810	5.6	20	30	35	
8	32	138	550	5.0	50	34	67	27

RESULTS

Sustained Hypotension Not Treated.—Eight dogs were bled as described until the arterial pressure was reduced to 30 or 50 mm. of mercury, and the duration of survival was noted. No effort was made to maintain the pressure at this level by reinjecting blood when it fell below 30 mm. of mercury. The longest period of survival was two hundred and sixty minutes and the shortest twenty minutes (table 1). Hematocrit determinations made when death seemed imminent showed an average reduction of 8 per cent in the volume of packed cells.

Further evidence of the narrow margin of safety which existed when this level of hypotension was maintained is the death of dogs during experiments in which treatment was contemplated but in which it was never begun because the dogs died before the minimum of forty minutes of hypotension had been completed or before the pressor response to angiotonin was reduced by less than 10 mm. of mercury.

Sustained Hypotension Treated by the Intra-Arterial Administration of All the Blood Removed.—After the period of hypotension, all of the blood that had been removed from the dog was returned by the intra-arterial method. The infusion was started by exerting 50 mm. of mercury pressure on the blood in the reservoir. Its effect on arterial pressure is exemplified in figure 2. One hundred to 175 cc. of blood usually entered the artery in the first two or three minutes.

and at the end of this time arterial pressure had increased sufficiently to exceed the infusion pressure of 50 mm. of mercury and stop the inflow of blood. After an interval of a few minutes infusion was resumed by increasing the pressure within the reservoir to 80 mm. and then to 120 mm. of mercury.

There were 12 experiments in this series and all of the animals but 1 (experiment 12, tables 2, 3, 4 and 5) survived.

When dogs with hypotension were treated by the intra-arterial method, the cardiovascular system usually failed to respond adequately if a pressure of more than 50 mm. of mercury was used in the blood reservoir to start the infusion. This failure was indicated by a sharp rise in intrathoracic venous pressure, of 10 to 15 cm. of water, and death ensued. Of 32 dogs in which the initial infusion pressure was 50 mm. of mercury the cardiovascular system failed to respond in only 2. To the first of these 400 cc. of blood was administered in seven minutes (experiment 12, tables 2 and 3), and the venous pressure increased 12 cm. of water but the arterial pressure did not rise above 50 mm. of mercury. The animal died within ten minutes after infusion was completed. To the second dog (no. 43, tables 6 and 7) 275 cc. of blood, which was one half of the blood removed,

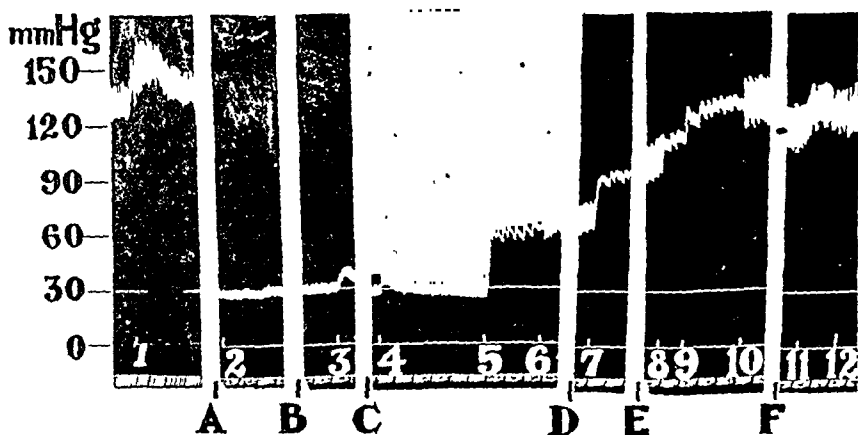


Fig. 2.—Experiment in which sustained posthemorrhagic hypotension was treated by intra-arterial infusion of all of the blood removed. The dog weighed 15 Kg. (experiment 11, tables 2 and 3). 1, 0.2 cc. of angiotonin; A, space represents an interval of sixty minutes during which 900 cc. of blood was removed by intermittent bleeding; 2, arterial pressure of 30 mm. of mercury—sustained hypotension begins; B, space represents thirty minutes of sustained hypotension; 3, 0.2 cc. of angiotonin administered after thirty-six minutes of sustained hypotension; C, space represents five minutes of continued hypotension; 4, 0.2 cc. of angiotonin; 5, intra-arterial infusion started with a pressure of 50 mm. of mercury in the blood reservoir; 6, infusion stopped by rising arterial pressure; 110 cc. of blood had been infused within three minutes; D, space represents interval of four minutes; 7, infusion started again by increasing pressure within the reservoir to 80 mm. of mercury; E, space represents an interval of nine minutes during which infusion was continued; 8, rising arterial pressure stopped infusion after 460 cc. of blood had been administered; 9, infusion continued by raising pressure within the reservoir to 120 mm. of mercury; 10, infusion of 800 cc. of blood completed in twenty-one minutes; F, space represents an interval of ten minutes; 11, 0.2 cc. of angiotonin administered twelve minutes after infusion; 12, venous pressure had been restored to prehemorrhagic level (maximum rise during infusion, 4 cm.).

was administered in five minutes. The venous pressure rose 13 cm. of water, and the dog died within two minutes after the infusion was stopped.

The effect of intra-arterial infusion on venous pressure was unpredictable. It could not be correlated directly with the rate of infusion. Thus, 68 cc. per minute for seven minutes caused a rise of only 2 cm. of water (experiment 25,

table 5) while 18 cc. per minute for thirty-three minutes raised the venous pressure 14 cm. of water (experiment 20, table 5). In general, the greatest change in the venous pressure was observed in those experiments in which large volumes of

TABLE 2.—*Production of Sustained Hypotension to Be Treated by Infusion of All of the Blood Removed (See Table 3)*

Experiment No.	Prehemorrhagic Period				Period of Intermittent Bleeding				Period of Hypotension				
	Weight, Kg.	Hematocrit Value, Mm.	Arterial Pressure, Mm. Hg	Response to 0.2 Cc. Angiotonin or 0.1 Cc. of Epinephrine Hydrochloride, Mm. Hg	Blood Removed, Cc.	Blood Removed, per Cent Body Weight	Change in Venous Pressure, Cm. Water	Time to Reach Sustained Hypotension, Minutes	Arterial Pressure		Duration, Minutes	Response to Angiotonin or Epinephrine at End of Period	
									Maximum, Mm. Hg	Minimum, Mm. Hg			
Dogs Recovered After Intra-Arterial Infusion													
9	10	30	138	36	605	6	—3	27	40	28	73	0	
10	9.3	36	122	22	450	4.8	—2.5	22	38	24	97	—2	
11	15	40	122	22	900	6	0	59	40	34	55	6	
Dogs Died After Intra-Arterial Infusion													
12	10	52	156	22	400	4	—7	38	30	20	68	0	
Dogs Recovered After Intravenous Infusion													
13	10.8	42	146	30	540	5	—2	18	46	38	70	10	
14	14	53	144	20	600	4.2	2	30	40	36	80	10	
				(Epinephrine)								(Epinephrine)	
15	13.3	34	150	40	728	5.5	—1.2	37	42	34	43	2	
16	10.2	40	122	36	625	6.1	—3.5	46	38	34	53	4	
17	10.5	46	126	26	640	6.0	—2.6	50	42	38	60	4	
18	10	44	108	28	610	6.1	—2.2	71	42	30	44	8	
Dog Died After Intravenous Infusion													
19	11.8	50	160	18	450	3.7	—2.0	50	52	38	65	0	

TABLE 3.—*Sustained Hypotension Treated by the Infusion of All of the Blood Removed*

Experiment No.	Period of Infusion				After Treatment	
	Arterial Pressure Infusion Begins, Mm. Hg	Blood Infused, Cc.	Time of Infusion, Minutes	Blood Infused per Minute, Cc.	Arterial Pressure, Mm. Hg	Response to 0.2 Cc. Angiotonin or 0.1 Cc. of Epinephrine Hydrochloride Solution, Mm. Hg
Dogs Recovered After Intra-Arterial Infusion						
9	28	535	8	66	134	8
10	24	450	20	24	118	16
11	34	800	20	40	126	10
Dog Died After Intra-Arterial Infusion						
12	22	400	7	57	0	
Dogs Recovered After Intravenous Infusion						
13	36	600	47	12	138	(Epinephrine)
14	40	550	75	7.3	116	
15	36	700	51	13	114	24
16	34	610	35	17	118	38
17	38	625	35	17	116	36
18	30	590	43	13	106	42
Dog Died After Intravenous Infusion						
19	38	425	55	7.7	102	(Angiotonin) 0

blood quickly entered the circulation without increasing arterial pressure over 50 mm. of mercury.

Sustained Hypotension Treated by Intravenous Infusion of All of the Blood Removed.—In 7 experiments (tables 2 and 3) sustained hypotension was treated

by returning intravenously all of the blood removed. The rate of infusion was governed by the intrathoracic venous pressure. If it suddenly rose more than 5 cm. of water the flow was reduced or stopped until it became stabilized. The

TABLE 4.—*Production of Two Periods of Sustained Hypotension in the Same Dog, the First to Be Treated by the Intra-Arterial and the Second by the Intravenous Method*

Ex- peri- ment No.	Method of Infusion	Weight, Kg.	Prehemorrhagic Period			Period of Intermittent Bleeding				Period of Hypotension			
			Hema- tocrit Value, Mm.	Arterial Pres- sure, Mm. Hg	Re- sponse to 0.2 Cc. Angio- tonin, Mm. Hg	Blood Re- moved, Cc.	Blood Re- moved, per Cent Body Weight	Change in Venous Pres- sure, Cm. Water	Time to Reach Sus- tained Hypo- tension, Min.	Arterial Pressure		Dura- tion, Min.	Response to 0.2 Cc. Angio- tonin at End of Period
										Maxi- mum, Mm. Hg	Mini- mum, Mm. Hg		
20	Arterial	10.3	..	136	20	600	5.8	-11	42	36	24	63	0
	Venous	10	38	130	26	595	5.9	-3	46	30	28	78	6
21	Arterial	14.2	50	160	16	660	4.7	-2.0	35	46	30	52	0
	Venous	12.0	49	118	14	665	5.5	-4.0	18	50	34	55	2
22	Arterial	14.6	42	158	18	520	3.2	-5.0	32	40	20	58	0
	Venous	13	40	136	16	575	4.1	-2.0	25	44	28	69	0
23	Arterial	11.7	34	152	34	650	5.5	-2.5	33	42	16	62	0
	Venous	11	50	178	18	640	5.4	-2.5	38	36	16	69	0
24	Arterial	10	30	130	20	600	6	-4	26	38	18	114	0
	Venous	10	45	132	12	472	4.7	-3	29	32	28	46	0
25	Arterial	12.5	32	142	18	500	4	-2.2	26	40	30	38	0
	Venous	10	30	118	28	300	3	-2.0	18	30	26	45	8
26	Arterial	13.5	44	174	16	905	6.6	-4.0	60	46	28	36	0
	Venous	11.6	39	150	20	350	3.0	-2.5	20	40	26	54	10
27	Arterial	10.8	49	120	28	570	5.3	-5.0	38	38	32	68	-12
	Venous	10.9	38	130	18	600	5.5	-2.0	28	40	30	68	0

TABLE 5.—*Sustained Hypotension Treated by Intra-Arterial and Intravenous Method in the Same Dog*

Experi- ment No.	Method of Infusion	Period of Infusion				After Treatment		
		Arterial Pressure Before Infusion, Mm. Hg	Blood Infused, Cc.	Time for Infusion, Minutes	Blood Infused per Minute, Cc.	Arterial Pressure, Mm. Hg	Change in Venous Pressure, Cm. Water	Response to 0.2 Cc. Angio- tonin, Mm. Hg
20	Arterial.....	26	600	33	18.1	130	14	11
	Venous.....	28	595	93	6.4	132	3	16
21	Arterial.....	30	500	13	38.4	110	6	12
	Venous.....	36	665	124	4.5	134	4	10
22	Arterial.....	32	500	27	18.0	122	6	12
	Venous.....	28	575	49	11	110	1.5	6
23	Arterial.....	30	580	10	58	118	9	18*
	Venous.....	26	170	15	11	0	5	
24	Arterial.....	18	530	27	19	122	6	12*
	Venous.....	28	192	28	6.8	0	10	
25	Arterial.....	30	480	7	68	122	2	18
	Venous.....	28	250	27	9.2	70	2	10
26	Arterial.....	28	600	21	28	120	5	22
	Venous.....	28	370	66	5.6	100	2.5	18
27	Arterial.....	32	500	14	35.7	120	11.0	
	Venous.....	30	600	100	6.0	110	2.0	8

* Dogs died during intravenous infusion.

average rate of flow was 12 cc., which was approximately one-fourth the rate of the intra-arterial infusion.

The arterial pressure rose slowly (fig. 3), but the level of pressure at the end was the same as after an intra-arterial infusion. The average time for the completion of the infusion was forty-nine minutes. Six dogs recovered, but the

seventh died one hour after the infusion. In the last-mentioned animal the arterial pressure at the end of the infusion was 102 mm. of mercury but began to decline as soon as the infusion stopped. Postmortem examination revealed typical visceral hemorrhages.

TABLE 6—*Production of Sustained Posthemorrhagic Hypotension to Be Treated by Returning One Half of Blood Removed*

Ex- peri- ment No	Weight, Kg.	Hema- to- crit Value, Mm.	Prehemorrhagic Period		Period of Intermittent Bleeding				Period of Hypotension					
			Arterial Pres- sure, Mm. Hg	Response to 0.2 Cc Angiotonin or 0.1 Cc of Epinephrine Hydrochloride (1.10,000)	Blood Re- moved, Cc	Blood Re- moved, per Cent Body Weight	Change Pres- sure, Cm Water	Time to Reach Sus- tained Hypo- ten- sion, Min	Arterial Pressure		Dura- tion of Hypo- ten- sion, Min	Response to 0.2 Cc Angio- tonin or 0.1 Cc of Epinephrine Hydrochloride Solution After Hypotension		
									Maxi- mum, Mm. Hg	Mini- mum, Mm. Hg		Angio- tonin	Epine- phrine	
Dogs Recovered After Intra Arterial Infusion														
28	14.2	26	158	14	18	545	3.8	-1.0	19	40	20	54	2	6
29	11.6	38	160	18	38	700	6	0	83	40	28	59	8	12
30	12.6	44	150	..	54	725	5.6	-6.0	44	40	30	106		8
31	9.5	37	144	..	28	578	6	-2.5	42	40	26	56		2
32	14	42	166	.	38	510	4	-3.0	55	36	28	65		0
33	9.4	40	142	.	44	605	6.4	-4.2	36	36	24	33		0
34	9	36	138	.	52	480	5.3	-3.0	34	38	28	34		2
35	12.1	40	118	.	26	670	5.5	-2.5	53	36	30	69		8
36	11.5	50	140	.	36	625	5.4	-3.0	92	36	32	62		8
37	12.0	44	140	.	34	632	5.2	-1.6	31	42	36	96		10
38	13.9	43	164	.	74	875	6.3	-2.3	115	36	24	33		0
39	12.5	47	194	.	22	610	4.8	-3.2	35	36	26	35		6
40	11.5	41	156	.	34	410	3.6	-2.5	50	36	26	46		4
41	10	46	148	.	80	525	5.2	-4.0	42	38	24	65		6
42	10.2	44	156	.	34	615	6	-3.0	57	38	28	40		2
Dogs Died Within Twelve Hours After Intra Arterial Infusion														
43	11	46	180	26	50	550	5	-1.5	45	38	30	45	4	6
44	12	38	148	16	.	560	4.6	-5	40	46	28	65	4	
45	11.2	55	138	.	46	760	6.7	-5.5	59	32	26	40		4
46	14.2	42	158	.	38	760	5.3	-8.0	43	36	30	71		12
47	11.6	36	182	.	18	500	4.3	-6.8	26	36	30	67		2
Dogs Recovered After Intravenous Infusion														
48	12.6	46	140	.	36	910	7.2	-5	64	34	28	40		0
49	14.1	42	148	.	44	850	6.1	-1.5	35	34	28	74		6
50	9.6	38	150	52	.	635	6.6	-4	57	46	30	63	8	
51	12	50	146	.	30	610	5	-2.4	43	38	28	46		6
52	10.5	40	126	.	44	400	4	-3	53	40	28	39		10
53	9.9	46	150	.	50	500	5	-5	63	38	26	57		6
Dogs Died After Intravenous Infusion														
54	12.3	42	138	30	30	834	6	0	83	34	28	59	8	12
55	10.5	44	138	.	40	580	5.6	-6	74	40	28	42		0
56	11	40	146	.	30	445	4	-1.7	41	36	28	41		8
57	13.4	36	120	..	28	700	5.2	-5	62	46	26	57		6
58	8.5	36	134	.	34	500	5.8	-3.0	77	30	20	40		0
59	12.4	44	160	.	26	620	5	-5.5	42	36	26	37		0
60	11.9	40	154	.	32	615	5	-4.7	24	46	20	41		8
61	10.3	36	130	.	44	420	4.2	-0.8	47	30	24	40		0
62	11.4	42	156	.	32	575	5.4	-3.5	34	38	24	44		4
63	9.3	44	136	.	42	760	4	-3.0	33	34	24	43		8
64	11.9	46	170	.	76	615	5.1	-4.6	53	30	26	41		6
65	9.3	55	176	.	26	472	5	-1.5	50	34	26	45		6
66	10.6	31	130	.	14	550	5.1	0	38	36	26	43		2
67	13.9	53	182	.	44	894	6.4	-4.5	66	32	24	40		6

Venous pressure was increased by a smaller volume of blood and a much slower rate of infusion when blood was given intravenously than when it was given by the intra-arterial route.

Comparison of Intra-Arterial and Intravenous Methods of Treatment in the Same Dog When All of the Blood Removed Was Returned—Because of the wide variations among most dogs, a more equitable basis for the comparison of these two methods was obtained by subjecting a dog which had recovered from sustained

hypotension treated by intra-arterial infusion to a second period of hypotension treated by the intravenous method. Eight dogs were treated in this manner (tables 4 and 5). An interval of at least two or three weeks elapsed between the first and the second period of hypotension. Every effort was made to

TABLE 7.—*Sustained Hypotension Treated by Infusion of One Half of Blood Removed*

Experiment No.	Period of Infusion				After Treatment				
	Arterial Pressure When Infusion Began, Mm. Hg	Blood Infused, Cc.	Time of Infusion, Minutes	Blood Infused per Minute, Cc.	Arterial Pressure		Response to 0.2 Cc. of Angiotonin or 0.1 Cc. Epinephrine Hydrochloride Solution (1:10,000)		Hematocrit Value, Mm.
					At End of Infusion, Mm. Hg	1 Hour After Infusion, Mm. Hg	Angio-tonin	Epine-phrine	
Dogs Recovered After Intra-Arterial Infusion									
28	20	270	9	30	88	90	18	22	..
29	28	355	10	35	120	122	12	22	..
30	30	360	14	25	116	120	..	30	48
31	26	285	12	23	96	110	..	26	42
32	28	250	10	25	90	106	..	18	46
33	24	300	12	25	122	90	..	16	46
34	26	235	8	29	130	132	..	26	38
35	30	335	8	41	72	94	..	30	32
36	32	310	8	38	90	94	..	20	48
37	36	315	9	35	98	120	..	18	46
38	28	440	14	31	100	130	..	28	46
39	24	305	15	20	146	160	..	20	42
40	26	200	5	40	96	76	..	26	40
41	24	260	6.5	43	138	140	..	28	48
42	28	305	7	43	100	126	..	20	44
Dogs Died Within Twelve Hours After Intra-Arterial Infusion									
43	28	275	5	55	69	0	0	0	*
44	30	255	8	31	86	110	0	..	42†
45	26	375	8	45	90	98	..	12	56‡
46	28	380	11	34	86	112	..	28	44§
47	30	250	5	50	110	102	..	6	46¶
Dogs Recovered After Intravenous Infusion									
48	28	455	78	5.7	102	106	..	8	56
49	28	435	58	7.5	140	132	..	32	42
50	30	315	46	7.0	122	136	32	..	50
51	28	300	26	8.5	90	118	22	30	46
52	28	200	16	12.5	108	94	..	20	46
53	26	250	45	5.5	110	112	..	26	50
Dogs Died Within Twelve Hours After Intravenous Infusion									
54	28	416	33	12	100	72	16	14	#
55	28	290	28	10	110	100	..	0	#
56	28	225	47	4.8	76	90	..	30	36
57	30	335	35	9.5	138	100	..	12	46#
58	20	250	30	8	0	0	34#
59	20	310	45	7.0	120	90	..	10	48#
60	20	310	22	14	70	70	..	12	4C#
61	24	210	31	6.8	82	86	..	30	
62	24	285	19	15	82	96	20	40	3C#
63	24	180	25	7.2	108	90	..	18	46
64	26	300	26	8.5	120	84	..	16	50
65	26	235	15	15	120	126	..	6	50
66	26	270	11	24	108	84	..	10	27#
67	24	437	13	33	122	122	..	8	56

* Dog survived thirty minutes after infusion.

† Dog survived eight hours after infusion.

‡ Dog survived five hours after infusion.

§ Dog survived twelve hours after infusion.

Dog survived less than six hours after infusion.

|| Dog survived twelve hours after infusion.

¶ Dog survived three hours after infusion.

reproduce in the second period the same conditions that had existed in the first. The duration of each period was determined by the time required to reduce the pressor response to angiotonin to less than 10 mm. of mercury. In all but 2 experiments the average duration of the second hypotensive period was six minutes more than the first.

All 8 dogs receiving the intra-arterial infusion recovered. Two dogs failed to do so when treated by the intravenous method, and in both of these death occurred before all of the blood removed could be returned.

The first dog which died during intravenous infusion (experiment 23, tables 4 and 5) had received 580 cc. of blood intra-arterially in ten minutes with no apparent ill effects, but only 170 cc. of the 640 cc. of the blood removed could be returned during fifteen minutes of intravenous infusion. The second dog (experiment 24, tables 4 and 5) had received 530 cc. of blood intra-arterially in twenty-seven minutes and recovered, but death occurred after 192 cc. of the 472 cc. of blood removed had been infused intravenously in twenty-eight minutes. The intravenous infusion could not have been administered more rapidly, because as it was venous pressure had suddenly risen 10 cm. of water, a rise which we took to be a sign of impending cardiac failure. In both dogs all the blood removed had been infused intra-arterially in less time than was now required for incomplete and ineffective intravenous infusion. Further, as we shall see, the proportion of

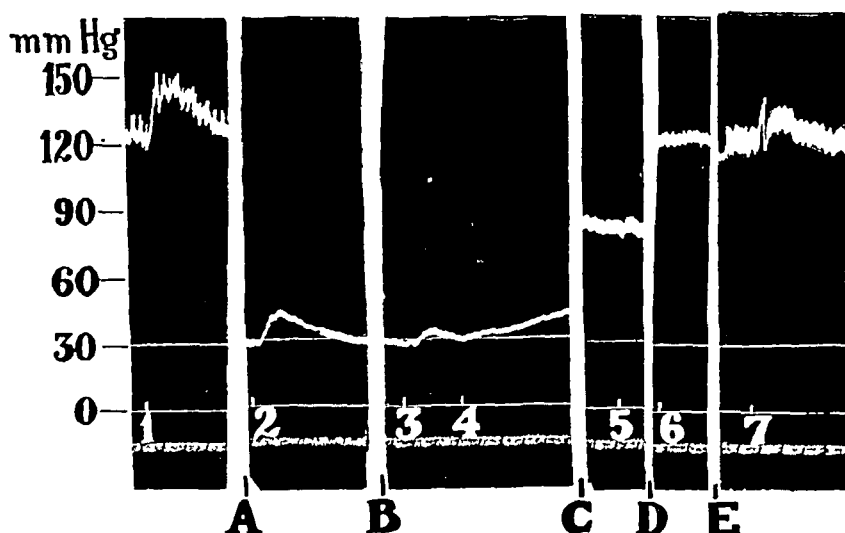


Fig. 3.—Experiment in which sustained posthemorrhagic hypotension was treated by intravenous administration of all of the blood removed. The dog weighed 10 Kg. (experiment 20, tables 4 and 5). 1, 0.2 cc. of angiotonin; A, space represents an interval of eighty-four minutes during which arterial pressure was reduced to hypotensive level by withdrawal of 595 cc. of blood in forty-six minutes and hypotension was maintained for thirty-eight minutes; 2, 0.22 cc. of angiotonin administered after thirty-eight minutes of hypotension; B, space represents an interval of forty minutes of continued hypotension; 3, 0.2 cc. of angiotonin administered after seventy-eight minutes of sustained hypotension; 4, intravenous infusion started; C, space represents an interval of twenty-three minutes during which infusion continued; 5, 200 cc. of blood had been infused in twenty-five minutes; D, space represents an interval of sixty-three minutes during which infusion continued; 6, infusion completed, 595 cc. of blood administered in ninety-three minutes; E, space represents an interval of twenty-five minutes; 7, 0.2 cc. of angiotonin administered twenty-eight minutes after infusion started.

the blood removed that was actually returned intravenously, if it had been given intra-arterially, would have raised the arterial pressure to nearly normal levels.

Comparison of the Efficacy of Intra-Arterial and Intravenous Infusions if Only One Half of the Blood Removed Was Returned.—In all of the preceding experiments in which the dogs recovered after intra-arterial infusion, 100 to 175 cc. of blood had been enough to raise the arterial pressure to at least 60 mm. of mercury; therefore it seemed likely that dogs could be saved if only a part of the blood that

had been removed was returned. In preliminary trials, the restoration of 19, 25 and 33 per cent was not sufficient to cause survival but infusion of 50 per cent resulted in recovery. In the dogs receiving less than 50 per cent, death occurred within four hours after the infusion had been completed.

Half of the blood withdrawn was returned intra-arterially in 20 experiments and intravenously in another 20 (tables 6 and 7). Arterial pressure in the first group of animals was quickly elevated above the initial infusion pressure in all experiments except 1 (experiment 43, table 7). In this experiment there was no response, and the dog died soon after infusion was stopped. In 4 experiments (nos. 44, 45, 46 and 47, tables 6 and 7) arterial pressure after infusion was more than 85 mm. of mercury. It began to decline within one or two hours, and the dogs were dead twelve hours later. Postmortem examinations revealed hemorrhages in the spleen, liver and intestines. The intestine contained serosanguineous fluid and the mucosa was hemorrhagic.

The remaining 15 dogs treated by the intra-arterial method recovered. Bloody diarrhea similar to that observed in the dogs in which sustained hypotension was not treated appeared in some dogs after arterial pressure had been restored by returning one half of the blood.

Of the 20 dogs treated by the intravenous method, only 6 recovered and 14 died within the first twelve hours after treatment. The arterial pressure failed to increase in only 1 dog, and this animal died (no. 58, tables 6 and 7). In the remaining 19 dogs it rose gradually during the infusion. It was as high as, and sometimes higher than, it was at the end of the intra-arterial infusion of the same proportion of blood. However, in 13 dogs the pressure was not maintained; 6 were dead within six hours, and the remaining 7 died within twelve hours. The postmortem observations were the same as those described for the dogs which died after intra-arterial infusion.

The Effect of Sustained Hypotension and Treatment by Infusion on the Pressor Response to Angiotonin and Epinephrine.—The use of epinephrine and angiotonin in tests of the effects on the vascular system of hypotension and of the efficacy of treatment proved to be of value on two scores: First, objective evidence was provided that vascular reactivity to angiotonin and epinephrine had been uniformly depressed by hypotension. Second, when the response to these substances was not restored by treatment all of the dogs died in twelve hours despite the fact that arterial pressure was at first elevated to normal levels by the treatment. However, restoration of response did not insure survival.

With respect to angiotonin, hypotension almost abolished the pressor response in 23 dogs and in 16 of these restoration of arterial pressure, regardless of the method of administering the blood, resulted in a return to responsiveness. Two of these dogs died, and 14 recovered. Of the 7 in which responsiveness did not return, all died within twelve hours. To save space, these results are not included in the tables.

The rate of loss of responsiveness to angiotonin and epinephrine was compared in 4 dogs (nos. 28, 29, 43 and 54, tables 6 and 7). Parallelism was definite in each.

The average response to epinephrine was reduced by the period of hypotension from 37 to 5 mm. of mercury in 37 dogs. Seventeen of these dogs died within twelve hours after infusion, 1 of them before the test could be made. A pressor response to epinephrine was obtained in 14, and was absent in 2 of them after treatment. Twenty dogs recovered and they all responded to epinephrine after treatment.

The Intra-Arterial Infusion of Plasma in Human Beings.—Three patients who were in profound post-traumatic shock received intra-arterial infusions of plasma. Before the infusion was started the blood pressure was less than 50 mm. of mercury in all of them. The arterial pulse was not palpable in any of the peripheral arteries. The radial artery was dissected out at the wrist and a 14 gage needle inserted. The needle was placed in the artery so that the infusion would flow toward the heart.

The inflow of plasma was very rapid for a few minutes, and the arterial pressure rose quickly, so that within five or ten minutes the blood pressure was 75 systolic and 40 diastolic in the first patient, 80 systolic and 35 diastolic in the second and 96 systolic and 40 diastolic in the third. This rapid rise in arterial pressure was associated with infusion of several hundred cubic centimeters of plasma. Arterial pulse was now palpable in the radial artery in the opposite arm.

Meanwhile, the heart rate decreased 10 to 20 beats per minute and the force of the apex beat definitely increased. As arterial pressure continued to rise, the systolic pressure exceeded the infusion pressure and inflow of plasma became intermittent. When the diastolic pressure exceeded the infusion pressure, the infusion ceased. At times the blood pressure forced blood out into the tubing and arterial pulsation could be seen in it.

All of the patients were treated surgically for their injuries. During the operations the arterial pressure was maintained by intermittent intra-arterial infusion. Five hundred to 1,000 cc. of whole blood in addition to plasma was administered to each patient. The blood pressure of all patients was at least 100 mm. of mercury systolic and 50 diastolic when the operations were completed. After five or six hours of intermittent infusion the needle was removed and the artery ligated.

One patient died of shock twenty-four hours later. The blood pressure in this patient could not be maintained by intravenous infusion after the arterial infusion had been stopped. The second patient died four days later, probably from a cause not directly related to shock. The third patient recovered.

In the patient who lived four days and in the one who recovered, an area of sloughing appeared on the flexor surface of the forearm which had been used for the intra-arterial infusion. This area paralleled the distribution of branches of the radial artery. The patient who recovered showed no other ill effect from ligation of the radial artery.

COMMENT

The apparatus and method of bleeding used in these experiments offer a convenient and practical means of producing severe, sustained hypotension with a minimal danger of bacterial contamination. Another important advantage of the technic is that excess citrate solution is not used. The dogs therefore will not at any time receive blood containing more citrate than is necessary to prevent clotting.

The narrow margin of safety at the low arterial pressure of 30 mm. of mercury necessitated arrangement of the apparatus so that blood could be returned quickly if arterial pressure began to fall below this level. After some practice, we were able to maintain it within ± 8 mm. of mercury of the desired level.

Courage is sometimes needed to withdraw enough blood so that too much time does not elapse before the level of 30 mm. of mercury is reached. In most experiments it was attained within forty minutes of the first hemorrhage and sustained for forty minutes or more.

Methods have not so far been devised for determining the severity of the effects of hypotension on the vascular system. For this reason we have used as a means of estimating these effects Page's¹ observation that hemorrhage reduces or abolishes the response to angiotonin and that restoration of normal blood pressure does not necessarily restore responsiveness. Epinephrine hydrochloride was also found to be of use and seemed to parallel the action of angiotonin, though it is perhaps not as sensitive. In most dogs the period of hypotension required to abolish the response was from forty to sixty minutes, but in a few more time was necessary. It is possible that angiotonin and epinephrine and other substances which test vascular reactivity may be used as a means of standardizing the effects of hemorrhagic hypotension.

One fact stands out clearly. When the response to angiotonin or epinephrine hydrochloride is not restored after treatment the chance of survival is very poor. However, the return of responsiveness does not guarantee survival.

The intra-arterial method has been used by Davis, Jermstad and Choisser² for administration of hypertonic solution of sodium chloride in the treatment of shock, but Kendrick and Wakim³ suggest that the solution may be deleterious. The pressor action observed was nervous in origin, since it disappeared on section of the spinal cord. Kendrick⁴ later found that 5 per cent solution of dextrose was more effective in experimental shock due to intestinal trauma when given by vein than by artery. These experiments, therefore, do not suggest that the intra-arterial method has any value as a mode for administering dextrose or hypertonic solution of sodium chloride. Administration of blood or plasma has apparently not been tried.⁵

The intra-arterial method for infusion of blood was first compared with the intravenous in a group of dogs in which all of the blood removed was returned. The results indicate the former has the one advantage over the latter of more rapid elevation of arterial pressure. The speed with which elevation is brought about probably enabled us to save 2 dogs of a group of 8. During a later experiment of the same nature the 2 survivors died after intravenous infusions.

Preliminary experiments conducted to ascertain roughly the minimum amount of blood it was necessary to return to insure survival showed that even by the intra-arterial route 25 to 35 per cent produced only a temporary rise in pressure. If 50 per cent was returned, 15 of 20 dogs recovered, and infusion of only 100 to 175 cc. of blood elevated the blood pressure to about 70 mm. of mercury in all but 1 of the animals. In contrast, only 6 of 20 of the animals treated intravenously with the same proportion of blood survived. It is interesting that the intravenous infusion raised the arterial pressure of 19 of the 20 dogs to 70 mm. of mercury or higher but in 13 of these the rise was only temporary and death occurred within twelve hours.

Measurement of intrathoracic venous pressure was used as a guide to the rate of administration of the infusions. If it rose more than 5 cm. of water the rate was reduced. It was found that if in the face of this warning the infusion was continued acute circulatory failure often caused death. Whether or not a rise in venous pressure would occur after the infusion was not predictable. Some animals were able to cope with large amounts of blood given rapidly

2. Davis, H. A.; Jermstad, R. J., and Choisser, R. M.: *Proc. Soc. Exper. Biol. & Med.* **37**:144, 1937.

3. Kendrick, D. B., and Wakim, K. G.: *Proc. Soc. Exper. Biol. & Med.* **40**:114, 1939.

4. Kendrick, D. B.: *Surgery* **6**:520, 1939.

5. After this paper was in press we found a publication by I. A. Birillo in a Russian journal (*Khirurgiya* **8**:3, 1939) in which the intra-arterial method was employed with success.

without an alarming rise, and others were not. In general, when a large volume of blood flowed in rapidly under a pressure of 50 mm. of mercury and no corresponding immediate rise in arterial pressure occurred, circulatory failure with rise in venous pressure might be anticipated.

To ascertain the practicality of administering blood or plasma intra-arterially to human beings, 3 patients in profound traumatic shock were treated by this method. The radial artery proved easy to cannulate, but the femoral artery is often easier. The difficulty with the latter is keeping the needle in place if the patient is not cooperative. From our experience with these patients we believe that the method is practical and might be used when insufficient plasma is available or arterial pressure is excessively low. In the latter circumstance it would seem wise to measure venous pressure and be guided by it for the rate of administration of blood or plasma.

SUMMARY

A method for producing hemorrhagic shock is described which produces severe sustained hypotension without increase of bacterial contamination or the use of excessive amounts of anticoagulants. Spontaneous recovery does not occur. An apparatus is described for return of the blood removed through an artery under controlled pressure.

The severity of the effects of the hypotension on the vascular system was ascertained by the pressor response to angiotonin or epinephrine. If the response is not restored after treatment the chance of survival is poor, but the return of responsiveness does not insure survival.

When all of the blood removed is returned by the intra-arterial route under a pressure of 50 mm. of mercury the systemic arterial pressure rises rapidly and recovery occurs. The same amount of blood given intravenously usually causes recovery, but not quite so certainly as blood given into the artery.

Readministration of only 50 per cent of the blood by vein resulted in recovery of 30 per cent of the dogs, while the same amount given intra-arterially resulted in recovery of 75 per cent.

When blood is given intra-arterially to animals with severe hypotension two precautions should be observed: 1. The pressure should not be greater than 50 mm. of mercury, and it should be elevated stepwise. 2. The rate of administration of the fusion should be guided by the venous pressure.

Intra-arterial infusions have been given 3 patients in severe shock to demonstrate the practicality of the procedure.

It is suggested that the method may have value when the amount of plasma or blood available is insufficient or when the arterial pressure is excessively low.

Mr. Clifford Wilson assisted in the experiments.

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BILATERAL CARCINOMA OF THE ADRENAL CORTEX WITH METASTASIS TO THE ILIAC BONE

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Carcinoma of the adrenal cortex is rare, and instances of simultaneous involvement of both adrenals are still rarer. In addition, metastases of such tumors to bone have been reported infrequently. These facts have led us to believe that a report of the following case may be of value:

REPORT OF A CASE

W. D., a white man 57 years of age, entered St. Luke's Hospital on March 17, 1939. His chief complaint was pain of six months' duration in the region of the right hip. He fell in September 1938 and bruised the right hip and since that time had had pain on movement, relieved at first by rest. The pain at times radiated along the right sciatic nerve. A punch biopsy was carried out at another hospital, but the report stated only that the patient had a "tumor." He had lost 19 pounds (8.6 Kg.). Just prior to his admission to the hospital there had been constant sciatic pain. There was localized tenderness in the inguinal region, so that the patient described it as "feeling like a boil." He admitted slight addiction to alcohol and said that he smoked two packages of cigarets a day. His usual weight had been 138 pounds (62.6 Kg.), and on admission it was 120 pounds (54.4 Kg.). The rest of his history was essentially noncontributory.

Physical examination: The patient was a well developed but undernourished middle-aged white man lying comfortably in bed. His breath had a strong alcoholic odor. The skin and mucous membranes were normal. The head showed no deformity and there were no areas of tenderness. The pupils were equal and reacted to light and in accommodation. Hearing was acute, and there was no discharge from the ears. There was no nasal obstruction or discharge. The mouth was edentulous; the tongue was clean and moist. Examination of the neck did not reveal any swelling or tenderness. The pharynx was clear. The chest was barrel shaped, and there was considerable limitation of expansion. The posterior portion of the chest on the right side was somewhat more prominent than on the left. The respiratory murmur was virtually absent over the entire posterior portion of the chest and noticeably diminished over the anterior portion. There were no rales. Fremitus and resonance were normal.

The heart was not enlarged; the peripheral vessels were somewhat thickened and the sounds distant. The rate and rhythm of the heart beat were normal. The blood pressure was 120 systolic and 74 diastolic.

Palpation of the abdomen revealed neither tenderness nor masses. The liver was at the costal border. The spleen was not felt. There were no scars. The genitalia were essentially normal.

There was definite evidence of pain in the region of the right hip when weight was borne on the leg. Motion in the hips was limited, and both great trochanters were prominent. There was a mass involving the right iliac crest and the right anterior superior iliac spine. The tumor was both deeply and superficially attached. The entire area involved was indurated but not particularly tender and measured roughly 8 to 10 cm. in diameter.

The right knee jerk was questionably present. The left knee jerk and both ankle jerks could not be elicited.

There was no deformity of the spine and no tenderness. Motion in the spine was normal. The urine was normal and its specific gravity was 1.024.

The blood count revealed a hemoglobin content of 95 per cent. There were 4,250,000 red cells and 12,000 white cells per cubic millimeter of blood. Sixty-four per cent of the white cells were polymorphonuclear leukocytes, 34 per cent lymphocytes and 2 per cent basophils.

From the Orthopedic and Pathologic Services of St. Luke's Hospital.

The Kline test for syphilis gave negative results

Roentgen examination on March 19, 1939 revealed a destructive process involving the right ilium. It extended from a point almost 2 cm. beyond the anterior superior spine downward to within 1 cm. of the acetabulum. The appearance suggested a tumor (fig. 1). Examination of the chest showed the heart, aorta and diaphragm to be normal. The pulmonary fields appeared clear (fig. 2).



Fig. 1.—Roentgenogram of the pelvis, showing a destructive lesion in the right iliac bone

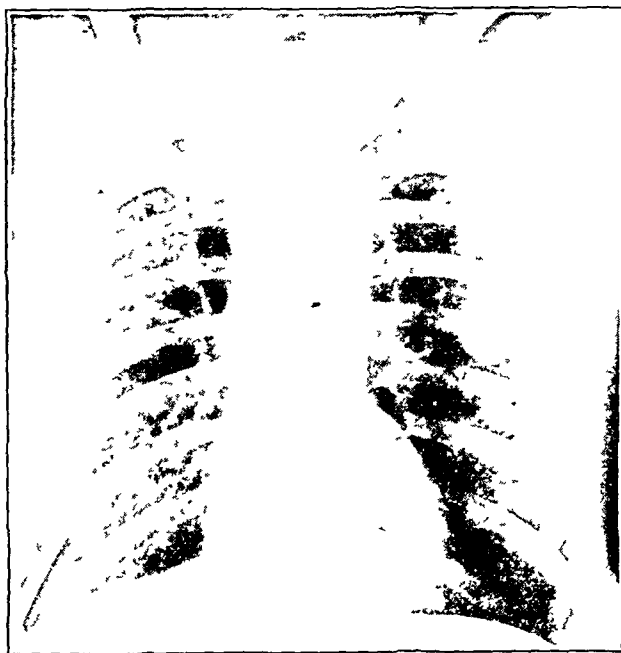


Fig. 2.—Roentgenogram of the chest, showing no evidence of metastatic carcinoma.

A preoperative diagnosis of neoplastic disease was made, and an exploration or biopsy of the tumor was proposed to determine the proper treatment.

The operation was performed on March 27, 1939. With the patient under cyclopropane anesthesia a 4 inch (10 cm) incision was made over the iliac crest and deepened to expose the tumor. Sections were removed and the wound was closed with interrupted silk sutures. The time of operation was twenty-five minutes.

At the site of the right iliac crest and below there was found a large mass of tissue which appeared necrotic. The iliac crest was replaced by cartilaginous-appearing yellowish tissue. After examining frozen sections the pathologist reported that the tumor was probably sarcoma. Because of the wide extent of involvement of the ilium and the soft tissues, no attempt was made to remove more of the mass of tissue than was necessary to identify its malignant nature.

Two hours after operation the patient had a rapid pulse, was sweating and had not reacted from the anesthesia. One hour later respirations were noted to be rapid, and the pulse was of poor quality. The extremities were cold. There was no bleeding from the wound. He was given an infusion of 1,500 cc. of 5 per cent solution of dextrose in physiologic solution of sodium chloride and blankets were applied and shock blocks placed under the foot of his bed. Three hours later his condition had improved but he had not become conscious. The following day his temperature rose from 101 F. at 8 a. m. to 105 F. at 12 p. m.

A medical consultant saw him at 11 a. m. and suggested the possibility of a cerebral accident and ordered an intravenous infusion of 100 cc. of 25 per cent solution of dextrose in physiologic solution of sodium chloride, which was given at 2 p. m. A roentgenogram made with portable apparatus showed no evidence of pneumonia. During the day he was given $\frac{1}{6}$ grain (0.01 Gm.) of morphine sulfate for restlessness. His pulse varied in rate between 120 and 130 and was of poor quality. His respirations rose during the day from 30 to 48 per minute. His last recorded temperature, at 4 a. m. on the second postoperative day, was 105.8 F. He died at 6:45 a. m., never having regained consciousness or rallied from shock after a simple operation.

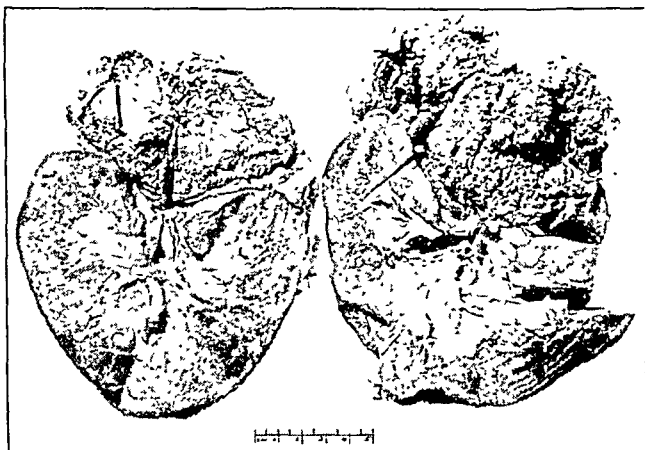


Fig. 3.—Photograph of adrenal tumors and kidneys.

Autopsy.—The body was that of an emaciated white man 57 years of age. Over the right superior iliac crest was an incision 11 cm. in length, made for removal of the biopsy specimen. Palpation in this region revealed loss of bone from the iliac crest and the region of the anterior superior iliac spine. The superficial cervical, axillary and inguinal lymph nodes were not enlarged.

The brain showed no lesions except moderate arteriosclerotic changes in the cerebral vessels. The pituitary appeared normal.

The right lung was collapsed and fixed to the wall of the chest by numerous fairly firm fibrous adhesions. There was no free fluid in either pleural cavity. The right lung was atelectatic, with occasional areas of bronchopneumonia. The left lung was relatively normal.

The entire gastrointestinal tract was free from gross pathologic changes.

The liver was free from tumor, the surface appearing generally pale with some chronic congestion. The gallbladder was normal, and the ducts were patent. The pancreas was normal in size and presented no gross lesions. The spleen weighed 175 Gm. and appeared normal.

The kidneys were normal in size; the capsules stripped with ease, and a fairly smooth surface was left. The corticomedullary markings were normal. In the right kidney immediately under the capsule and replacing the cortex was a small spherical encapsulated tumor, 1.5 cm. in diameter, pale gray, firm and of homogeneous structure. The ureters and bladder presented no pathologic changes.

The bodies of the vertebrae showed no invasion by the tumor.

The lymph nodes along the course of the aorta and iliac vessels were not enlarged.

The adrenals were both practically destroyed and had been replaced by thinly encapsulated tumor masses, the right being 7 by 7 by 5 cm. and the left slightly smaller (fig. 3). They were entirely distinct from the kidneys and adjacent fat. The tumors were discrete and rather soft and on section were extremely friable. They were composed of pale grayish white tissue without definite fibrous structure or noticeable vascularity. The normal adrenal markings were not recognizable, and in cross sections only a few minute areas of orange-pigmented cortex could be detected. No medulla was found.

In the anterior part of the right iliac bone the hemorrhagic cavity formed by the removal of tissue for biopsy was found filled with blood clots. The adjacent bone was soft, friable and obviously infiltrated by tumor over an area 4 by 6 cm. Outside the bone large, soft lobulated masses of tumor extended down through the gluteus medius muscle. Here the growth was white, opaque and homogeneous except for a few hemorrhagic areas (fig. 4).

Anatomic Diagnosis.—Bilateral adrenal carcinoma; metastasis to right iliac bone and adjacent muscles; adenoma of right kidney; bronchopneumonia.

Microscopic Examination.—No normal adrenal tissue was found, both cortex and medulla being replaced by masses of large flat cells, often detached and mostly without a well preserved cell membrane. Many presented a ragged or crushed appearance. Elsewhere they seemed to be growing in sheets, very loosely joined together. The cell bodies were in general somewhat polygonal with short blunt processes, but some were narrow and elongated (figs.

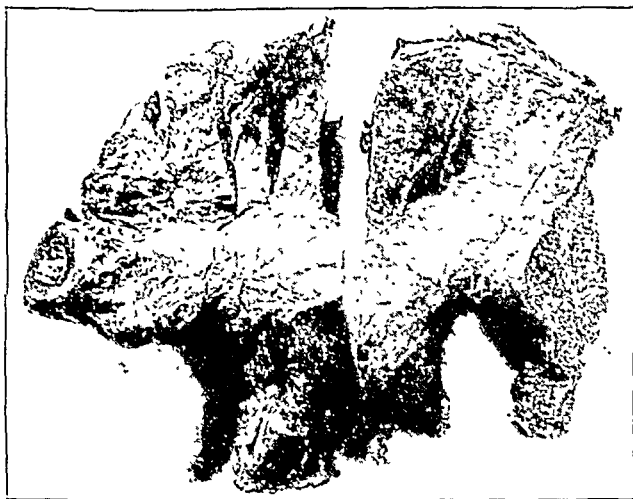


Fig. 4.—Photograph of the ilium, part of the ischium and the pelvic bone, showing the site of metastasis involving the iliac crest and the body of the pelvic bone.

5 and 6). The cytoplasm was slightly hydropic or homogeneous with the eosin stain. There were no collagenous fibrils extending from or between the cells. The yellowish streaks noted in the gross showed intracellular and extracellular orange-colored granular pigment, possibly the remnants of the adrenal cortical cells. Stains for fat revealed no lipid material.

The nuclei were often very large but showed wide variations in size and shape. There were some oval cells and other lobulated or giant forms. Nearly all were vesicular with a prominent nucleolus. Mitoses were infrequent, but the largest cells usually contained masses of deeply stained chromatin or exhibited bizarre degeneration forms.

There was no special alveolar or perivascular arrangement, no papillary structure and practically no interstitial connective tissue. Blood vessels were infrequent, only a few small venous channels being intact. There were some fresh hemorrhage and many large areas of necrosis. Tumor emboli were present in the blood vessels of the capsule. There was no resemblance to cells of the outer layers of adrenal cortex, but the structure of the inner reticular zone was still preserved, there being a loosely whorled or distorted stellate pattern in which the cells appeared to be attached at one pole.

It would be impossible to state in which adrenal the tumor first arose, but since the tumor on the right side was somewhat the larger, it was perhaps older. Bilateral tumors of the adrenals, like those of other paired organs, are usually regarded as independent growths arising simultaneously under the same stimulus. Bilateral metastases do of course occur.

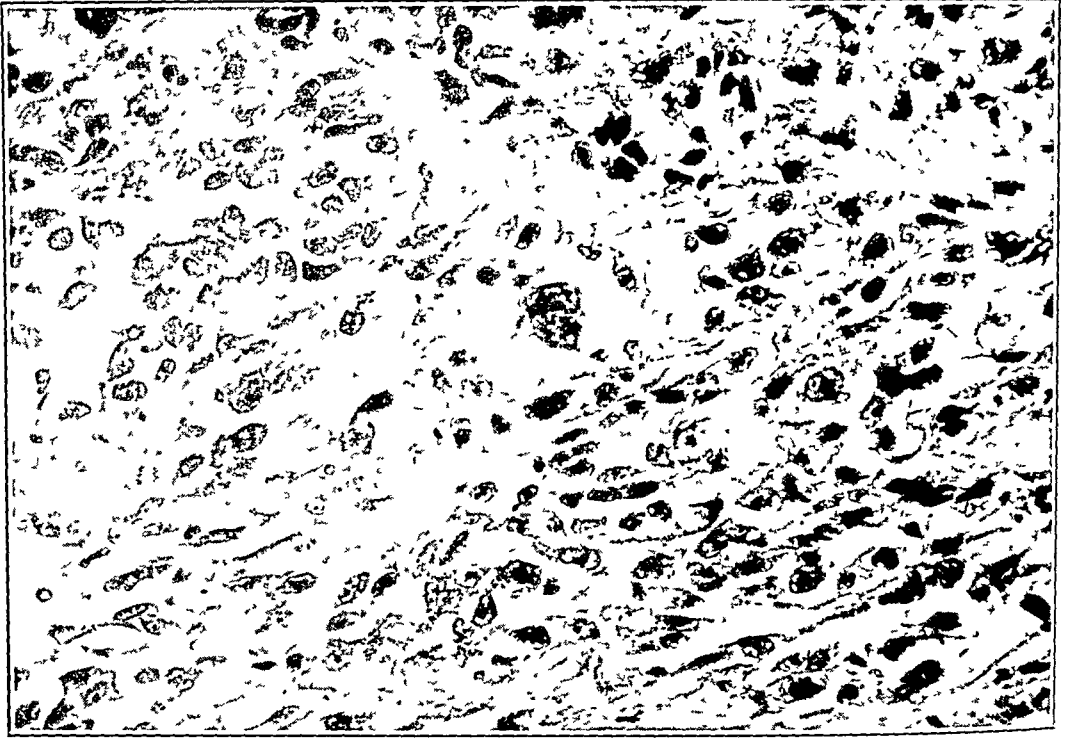


Fig 5—Photomicrograph of an adrenal carcinoma, showing loosely attached, elongated cells with reticulated pattern. The nuclei are generally large but show wide variations in both size and shape ($\times 300$).

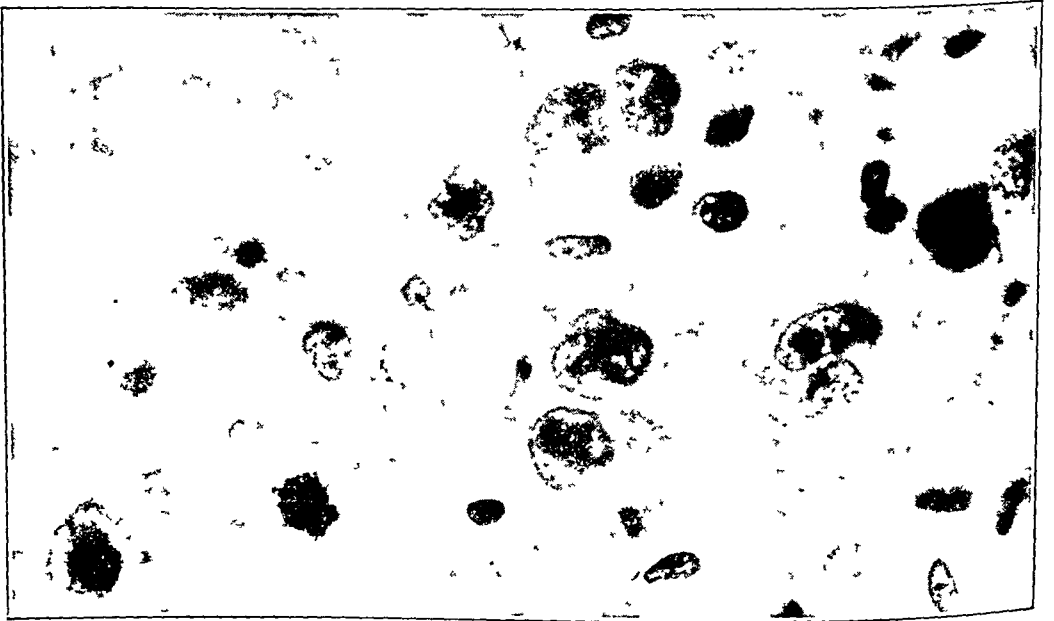


Fig. 6—High power photomicrograph of an adrenal carcinoma, showing granular and vacuolated cells and large irregular nuclei ($\times 700$).



Fig. 7.—Photomicrograph of bone from the ilium, showing metastatic tumor with necrosis of the bone ($\times 200$).

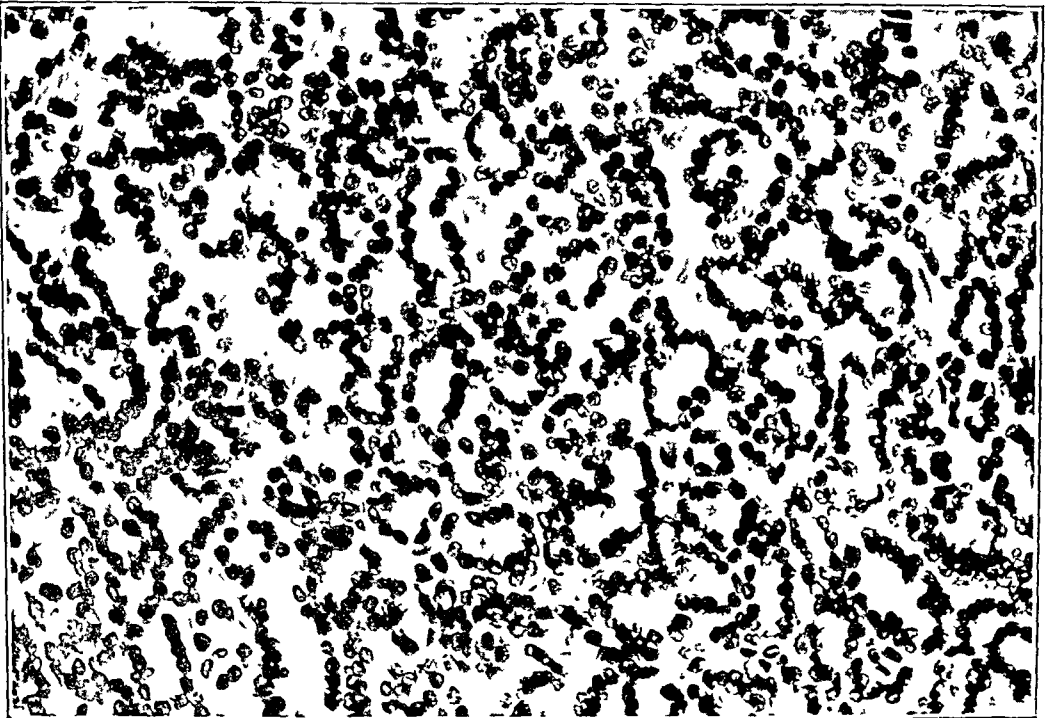


Fig 8—Adenoma of the right kidney Small compact epithelial cells line the tubules ($\times 300$).

usually when the retroperitoneal lymphatics are widely involved, as in the late stage of renal or pancreatic carcinoma, or they may even originate from the hilus of the lungs when bronchogenic tumors are present.

It must be noted that in this case metastases to the lymph nodes, involvement of the fatty or fascial tissue between the two adrenals and pulmonary metastases were absent. The only secondary tumor was that in the iliac bone.

Microscopic examination of the biopsy tissue restudied in juxtaposition with the material taken from the ilium at autopsy indicated that the large cells at first suggestive of sarcoma were actually the same as those of the adrenal tumors. They were not derived from osteoblasts, nor did they have characteristics of any myeloid cells. They invaded the marrow spaces, replacing fat and connective tissue with masses of large, often detached cells, poorly vascularized and showing much necrosis. Osteoblasts had disappeared (fig. 7), and the bone was undergoing necrosis.

Sections of the small cortical tumor of the right kidney showed it to be an adenoma unrelated to the adrenal neoplasm. It had a definite papillary structure and was composed of compact, deeply stained epithelial cells which formed small glandular structures resembling renal tubules (fig. 8). The cells were uniform and their arrangement regular. The size of this tumor was rather unusual, since growths of this type are seldom more than a few millimeters in diameter.

Sections of the pituitary revealed normal cells, and no significant changes were found in either the anterior or the posterior lobe.

Microscopic examination of the other organs did not disclose metastases or other significant lesions. Early bronchopneumonia was present in portions of the lung.

The cortical cells of the adrenal, while mesodermal in derivation, take on in the course of their development the form and functions of specialized epithelium; hence the tumors derived from them are usually called carcinoma.

The final diagnosis was bilateral carcinoma of the adrenal cortex, reticular type, with metastasis to the right iliac bone and the gluteal muscles and adenoma of the right kidney.

COMMENT

Interest in this group of neoplasms was awakened in 1896 by the publication in the *Edinburgh Hospital Reports* of a paper by Affleck and Leith¹ describing a tumor which occurred in a man 46 years old suffering from weakness and stiffness of the legs and back and complaining of loss of weight for a year, with pain for three months. There was no pigmentation of the skin. At autopsy a soft, pale yellowish white tumor was found in the right adrenal. The left adrenal contained a similar but smaller growth, and there were widespread metastases. The next year Kelyack² reviewed 26 cases of cortical tumors of the adrenal collected from the earlier literature, while only a year later Rolleston and Marks³ published a survey of all of the previously reported cases and attempted to distinguish the adenomas from the carcinomas. Only 14 were thought by these authors to be unmistakable carcinomas. There was, however, at this time no realization of the frequency of metastases of bronchial tumors to the adrenal, so that one may question whether some of these nonpigmented tumors were not metastases. In 1904 Hartmann and Lecène⁴ again reviewed the subject, giving special attention to a tabulation of the sites of metastases in all of the patients who came to autopsy, but after this comparatively little was added to the subject until about 1930, when important advances in endocrinology brought forth case reports of patients who showed the remarkable biologic effects due to hormones secreted by adrenal

1. Affleck, J. O., and Leith, R. F. C.: Clinical Observations on a Case of Sarcoma of the Suprarenal Capsules, *Edinburgh Hosp. Rep.* 4:278, 1896.

2. Kelyack, T. N.: Adrenal Growths, *M. Chron.* 7:401, 1897.

3. Rolleston, H. D., and Marks, H. W. J.: Primary Malignant Disease of the Suprarenal Bodies, *Am. J. M. Sc.* 116:383, 1898.

4. Hartmann, H., and Lecène, P.: Les tumeurs de la capsule surrénale, in Hartmann, H.: *Travaux de chirurgie anatomo-clinique*, Paris, G. Steinheil, 1904, series 2, pp. 14-43.

tumors. Unfortunately, even yet few of the cases have been studied both from the biologic and from the morphologic point of view.

Especially noteworthy for the clinicopathologic data are the recent paper of Lescher and Robb-Smith⁵ and that of Cahill, Loeb, Kurzrok, Stout and Smith.⁶ The latter includes reports on 4 patients who came to operation and the autopsy record of a patient seen in the terminal stage of the disease. Of the surgical patients 1 was living and well at the time of the report, about a year after operation; 2 died of metastases ten and twenty-seven months after operation, and 1 succumbed thirty-six hours after operation. This paper contains a full discussion of the clinical observations in these cases and an excellent review of the subject.

We feel that it is still doubtful whether the adenomas can always be morphologically distinguished from carcinomas. In the adrenals, as in other endocrine glands, especially the thyroid, metastasizing tumors arise whose structure is still that of a benign growth or even of hyperplasia, without definite indication of a neoplasm. Some of these tumors, as in the remarkable cases of Calder and Porro,⁷ Ashe,⁸ Feinblatt⁹ and Lukens, Flippin and Thigpen,¹⁰ have so interfered with metabolism as to cause death. Hence we include here some tumors described as adenomas since metastases were not present, even though a number of them proved rapidly fatal. Other tumors appear to have been cured by operation, and the patients were still well at the time of the report.

Our review of 49 cases from the literature shows that 18 of the tumors occurred in men, 23 in women and 8 in children under 14. Of the 23 women, 12 were in the fourth decade. Six of the 17 men whose age was given, the largest number in any one age group, were in the fifth decade, slightly older than most of the women. Tumors in girls aged 23 months and 3, 7½, 9, 11 and 13 years have been described by Walters,¹¹ Ashe,⁸ Little,¹² Lawrence¹³ and Babonneix, Delarue, Golé and Jourdan.¹⁴ In boys under 14 these tumors are even more rare. Player and Lisser¹⁵ reported one in a boy 4 years of age who was well twenty months after operation. The patient of Fordyce and Evans¹⁶ died twelve hours after operation and was found at autopsy to have metastases to the liver and the brain.

5. Lescher, F. G., and Robb-Smith, A. H. T.: A Comparison of the Pituitary Basophilic Syndrome and the Adrenal Corticogenital Syndrome, *Quart. J. Med.* **4**:23, 1935.

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15. Player, L. P., and Lisser, H.: Adrenal Sexual Precocity Caused by Tumors of Adrenal Cortex, *Urol. & Cutan. Rev.* **37**:758, 1933.

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Carcinoma of the adrenal cortex is occasionally bilateral, but some of the reported cases were not instances of primary carcinoma. The growth in Rosenstein's¹⁷ case, for example, was apparently some type of sarcoma.

The tumor described by Affleck and Leith¹ was also bilateral, but there was such extensive invasion of the retroperitoneal tissues that the two masses nearly met in the midline. In the case of Rimbaud¹⁸ the right adrenal was grossly involved, and microscopic examination revealed that the left had also been invaded. Grynfeldt and Rimbaud,¹⁹ Weinberg and Turquet²⁰ and Kimm and Wu²¹ also described bilateral tumors. The last-named authors observed widespread metastases.

Among the 49 cases, therefore, we have found only 5 in which the tumors were bilateral, and in 4 of these the growths may have been secondary. The case of Kimm and Wu²¹ was the only one closely resembling that reported here.

In studies of solitary tumors the condition of the opposite adrenal has been the subject of considerable interest. Lukens' patient with a solitary adenoma of the right adrenal was found at autopsy to have no left adrenal. The same abnormality was found in Feinblatt's⁹ patient with a carcinoma in the right adrenal. Grynfeldt and Rimbaud¹⁹ described a tumor arising from the zona fasciculata of the left adrenal. It was only moderately enlarged, while the right adrenal was hypertrophied. More often, however, the opposite adrenal has shown atrophy, as in the cases of Calder and Porro⁷ and Little¹² and the second case of Lawrence.¹³

In the 40 cases in which we are reasonably sure of the site of origin, 14 tumors have been primary on the right side and 26 on the left.

The symptoms are extremely variable, since the specific biologic effects of abnormal hormones may or may not be present. Fewer symptoms are usually present if the patient is a male. Ten of 18 adult male patients showed no sexual abnormalities, while only 3 of 23 females were without structural sexual alterations. Before puberty such alterations may be absent, as in Ashe's⁸ case of a girl 3 years of age who had an adenoma of the cortex associated with hypertension and cyanosis but who did not show unusual secondary sexual development.

In women the syndrome closely resembles that of Cushing's pituitary basophilism in that there is a diminution of the female characteristics associated with the appearance of certain male ones. Amenorrhea, obesity or loss of weight and changes in the skin (usually acneform coarsening and increase in the oily secretion), accompanied with hypertrichosis and striae, are frequent. Polycythemia with dusky red or cyanotic face or extremities, hypertension and headache are often present. Masculinization is shown by hypertrophy of the clitoris and masculine growth and distribution of hair on the face, trunk and extremities. In some cases extreme changes have taken place in the general habitus. In the male the syndrome is usually less well defined than in the female. Simpson and Joll²²

17. Rosenstein, S.: Sarcom der Nebennieren mit Metastasen in Nieren, Pancreas und rechtem Herzen, *Virchows Arch. f. path. Anat.* **84**:322, 1881.

18. Rimbaud, P.: Syndrome addisonien à évolution rapide. Epithélioma cortical des capsules surrénales, *Bull. et mém. Soc. méd. d. hôp de Paris* **49**:404, 1933.

19. Grynfeldt, E., and Rimbaud, P.: Adénome cortical des capsules surrénales. *Bull. Assoc. franç. p. l'étude du cancer* **21**:614, 1932.

20. Weinberg and Turquet: Cancer des deux capsules surrénales avec noyau métastatique du cervelet. Mort subite, *Bull. et mém. Soc. anat. de Paris* **72**:751, 1897.

21. Kimm, H. T., and Wu, S. D.: Bilateral Adrenal Cortical Carcinoma, *Chinese M. J.* **59**:195, 1941.

22. Simpson, S. L., and Joll, C. A.: Feminization in a Male Adult with Carcinoma of Adrenal Cortex, *Endocrinology* **22**:595, 1938.

discussed 6 cases of the condition in men, in all of whom female characteristics were noted. Hypertrophy of the breasts was the first symptom in 4 patients, and in 3 it was associated with atrophy of the testes, loss of libido and gain in weight.

With the continued growth of the tumors remarkable skeletal changes may occur. Osteoporosis, especially in the bones of the skull and trunk, is rather frequent, but overgrowth of these bones may also take place. Extreme deformities due to fractures and compression of the bodies of the vertebrae may be associated with only slight involvement of the long bones of the extremities. Lescher and Robb-Smith⁵ found osteoporosis also in 9 of 14 cases of basophilic adenoma studied at autopsy. The affected bones of patients with carcinoma of the adrenal cortex show no extensive fibrosis or accumulation of granulation tissue, such as occurs with osteitis fibrosa cystica, but there is extensive irregular atrophy of all bony trabeculae and of the cortex with at times some minute cysts and some dense osteoid tissue. The condition of the bone marrow varies. In the case of Calder and Porro⁷ it was largely fatty, although the patient had a dusky red skin, but in the case of Lescher and Robb-Smith,⁵ whose patient had been conspicuously cyanotic, the bone marrow in the middle third of the femur showed erythropoietic hyperplasia.

In spite of the general decalcification and multiple fractures the calcium content of the blood may be little altered. For instance, in the patient of Calder and Porro⁷ the calcium content of the blood was 10 mg. and the phosphorus content 2.6 mg. per hundred cubic centimeters. In Lukens'¹⁰ patient the calcium content of the blood was 10.4 mg. and the phosphorus content 3.4 mg. per hundred cubic centimeters. The value for phosphatase activity was 32 units. The patient of Kimm and Wu²¹ had widespread osteolytic changes and the calcium content of the blood was 5.9 mg. and the phosphorus content 4.7 mg. per hundred cubic centimeters.

Tests for sex hormones in patients with adrenal carcinoma were reported in 1934 by Frank,²³ who found excessive amounts of estrogenic substance in the urine. Cahill⁶ did not find large amounts in the tests on his patients, but much work remains to be done in this field.

In diagnosis, the exclusion of pituitary disease with or without tumor offers the greatest difficulty. Gamna and Forconi²⁴ in a survey of 39 patients with Cushing's syndrome found that 14, or 35 per cent, had no pituitary disease and that of these 14, 5, or 12.5 per cent of the total number, had tumors of the adrenal cortex. Graef, Bunim and Rottino²⁵ reported a case of adrenal carcinoma with coexistent pituitary adenoma.

Lawrence¹³ stated that changes in the voice are always produced by adrenal tumors but not by pituitary tumors. Calder and Porro⁷ emphasized the fact that although hypertrophy of the genitalia is not present in pituitary basophilism, its absence does not establish the diagnosis.

The prognosis in this group of carcinomas of the adrenal cortex is obviously poor; since they metastasize readily by way of the blood stream and grow rapidly, the duration of life without operation is short. Operation, though the mortality rate is high, has been successful in several cases. Walters and Kepler¹¹ at the

23. Frank, R. T.: A Suggested Test for Cortical Adrenal Carcinoma, *J. A. M. A.* **109**:1121 (Oct. 2) 1937.

24. Gamna, C., and Forconi, A.: Sulla patogenesi della distrofia adiposo-genitale osteoporotica (Morbo di Cushing), *Minerva med.* **1**:201, 1936.

25. Graef, I.; Bunim, J. J., and Rottino, A.: Hirsutism, Hypertension and Obesity Associated with Carcinoma of the Adrenal Cortex, *Arch. Int. Med.* **57**:1083 (June) 1936.

Mayo Clinic removed 5 of 7 of these tumors. The other 2 were infiltrating and hence inoperable. Three of Cahill's 4 patients⁶ also recovered from operation, and Lawrence,¹³ Player and Lisser,¹⁵ Neumann²⁶ and Holl²⁷ have also reported successful extirpations with survival after operation for variable periods. Of a total of 40 patients who underwent operation about 50 per cent died very shortly. Lukens¹⁰ stated that most fatalities occur within the first forty-eight hours. Walters and Kepler¹¹ expressed the opinion that when active, well directed post-operative treatment with adrenal cortical extract, sodium chloride, sodium citrate and sodium bicarbonate and a low potassium diet is carried out the surgical risk is not too great. The outstanding symptoms of adrenal insufficiency appear within eight hours after operation and include rapid pulse, fall in blood pressure, drowsiness, hiccups, nausea and vomiting. Insomnia, anorexia, weakness, apathy and restlessness may follow. Weil and Browne²⁸ stated that the adrenal cortex hormone is excreted in increased amounts after operations which do not involve the adrenals and that increased quantities of it appear postoperatively in the urine, the maximum being reached by the third to the fifth day. It is easy to believe, then, that the margin of safety of the patient with seriously damaged or atrophied adrenals is very low.

Metastases, if one may judge from the somewhat meager clinical records and from the data obtained from 18 autopsies, are most frequent in the lungs, liver and lymph nodes. The adrenal veins and the vena cava have been found involved. Less frequent are metastases to the brain, kidney, heart, peritoneum and pancreas. In contrast to the hypernephromas of the kidney, which readily metastasize to bone, the carcinomas of the adrenal have only infrequently been found to do so. In 1 other case, that of Kimm and Wu,²¹ metastases were present in the iliac bone, as in our case, as well as in the vertebrae, ribs and scapula. When roentgenograms are studied it should be noted that the frequency of widespread decalcification and crushing is greater than that of skeletal metastases.

SUMMARY

A case of bilateral carcinoma of the adrenal cortex with metastasis to the right iliac bone has been presented. This patient showed no sexual abnormalities, such as have sometimes been reported in other patients with similar lesions. The tumor was recognized as a malignant growth involving the ilium. The cause of the patient's complete collapse after an extremely simple operative procedure was unrecognized before death, although he presented the classic signs of insufficiency of the adrenal cortex. Fortunately this clinical failure could not by any stretch of the imagination have affected the eventual outcome.

115 East Sixty-First Street.
St. Luke's Hospital.

26. Neumann, H. O.: Nebennierenrinde und Geschlechtlichkeit, Arch. f. Gynäk. **160**:481, 1936.

27. Holl, G.: Zwei männliche Fälle von Nebennierenrindentumoren mit innersekretorischen Störungen, Deutsche Ztschr. f. Chir. **226**:277, 1930.

28. Weil, P., and Browne, J. S. L.: The Excretion of Cortin After Surgical Operation, Science **90**:445, 1939; A Cortin-like Action of Extracts of Human Urine, Am. J. Physiol. **126**: 652, 1939.

CONFINEMENT TO BED FOR ONLY TWENTY-FOUR HOURS AFTER OPERATION

A MEANS OF PREVENTING PULMONARY AND CIRCULATORY COMPLICATIONS
AND OF SHORTENING THE PERIOD OF CONVALESCENCE

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DETROIT

As a result of getting patients out of bed on the first postoperative day and increasing their activity as tolerated (with respiratory exercises mentioned herein-after), circulatory and pulmonary complications have been reduced to a minimum, intestinal function has been restored without enemas and the period of morbidity and disability has been diminished 50 per cent or more.

A previous publication¹ on this subject precipitated editorial comments in several leading medical journals.² These comments enable me to correct erroneous impressions surgeons inexperienced with early rising have had regarding it. In addition I am presenting another series of 464 consecutive surgical cases in which practically all the patients were subjected to early rising.

This article also brings to attention specific reflexes that initiate pathologic changes—changes that lead to complications—and presents evidence that early rising, with its modifying effect on these reflex reactions, should be instituted by the first postoperative day.

Members of the medical profession have often inquired: "What stimulated interest in twenty-four hour confinement to bed after surgical procedures; and is there scientific evidence to support the theory that limiting confinement to bed to twenty-four hours is a means of preventing pulmonary, circulatory and other complications?" This study presents the scientific evidence, and the following case history is a reply to the first query.

In 1938, Mr. R. H., aged 38, disregarded orders and left his bed frequently a few hours after an appendectomy. Improvement was rapid as a result of frequent ambulatory activity, and on the following day he insisted on leaving the hospital. I was unable to convince him of the "danger" of such a procedure, and he left at his own risk. On the second post-operative day he drove 30 miles to run errands in busy downtown Detroit; on the third and fourth postoperative days he worked in the garden; on the fifth day he drove 40 miles for his first medical inspection following the operation. He was in excellent condition. This unusually rapid convalescence aroused my interest.

Unaware that the principle of early rising had been previously applied by surgeons here and abroad, I was so stimulated by this incident that thereafter I saw that practically all patients were got out of bed on the first day after an appendectomy and were permitted to leave the hospital the same afternoon, if they so desired, provided distention, abdominal rigidity or some other contraindication was not present. After a long and most gratifying experience with early rising after appendectomy, I applied the principle in other fields of abdominal surgery, and finally began to employ the method with all surgical patients, including those with

1. Leithauser, D. J., and Bergo, H. L.: Early Rising and Ambulatory Activity After Operation: A Means of Preventing Complications, *Arch. Surg.* **42**:1086-1093 (June) 1941.

2. Early Rising After Operation, editorial, *New England J. Med.* **226**:576-577 (April 2) 1942. Early Rising and Ambulatory Activity After Operation, editorial, *M. Times* **69**:440-441 (Oct.) 1941. Early Rising After Operation, Current Comment, *J. A. M. A.* **117**:1710 (Nov. 15) 1941.

ruptured appendixes. In each field of surgery, every patient operated on since early rising was instituted, whether subjected to this treatment or not, is reported on in this article.

A REVIEW OF THE LITERATURE

Early rising following celiotomy was first practiced routinely by Ries³ over forty years ago. He was enthusiastic about this advantageous method of postoperative care. Most of his patients, including those operated on for hernia, were out of bed on the second day. He emphasized that eventration was not more common than when prolonged confinement to bed was insisted on. Binders were not employed, but adhesive straps were applied to infected wounds. However, the practice did not gain support until the late twenties, and then only in foreign lands.

Twenty-nine of the foreign articles have been studied and condensed for this review. Two patients who died of embolism were reported by Cotte.⁴ Both were out of bed on the third day; one died on the fifth day and the other on the eighth day. However, Cotte stated that death in the latter case may have been due to heart failure. Chaliér⁵ was an enthusiastic exponent of early rising but was bitterly opposed by Violet⁶ and Villard.⁷ The latter presented at a meeting 2 unpublished cases of fatal embolism following early rising reported to him by a colleague. Chaliér⁸ analyzed these 2 cases and intimated that since neither Villard nor his colleague had any experience with early rising, their opinions must be considered in that light. Chaliér reported 150 cases in 1929 and 606 cases in 1932.⁵ His patients were out of bed between the third and the fifth day. He found no report in the literature that the practice had been discontinued because of ill effects. Zillmer⁹ in 1930 reported on 524 patients who were out of bed on the first postoperative day. In 1935 Charbonnier¹⁰ reported on 112 patients out of bed between the third and the fifth day. In 1935 Gullotta¹¹ reported 498 cases; some of the patients were out of bed on the second day. Coniglio¹² reported 151 cases, Salishchev and Ayziks¹³ 194, Florcken¹⁴ 219 and Ricci¹⁵ 180. Other exponents

3. Ries, E.: Some Radical Changes in After-Treatment of Celiotomy Cases, *J. A. M. A.* **33**:454-456 (Aug. 19) 1899.

4. Cotte, G.: Fatal Embolism on the Eighth Day in a Woman Who Rose Early, *Lyon chir.* **36**:441 (July-Aug.) 1939.

5. Chaliér, A.: Early Rising After Abdominal Operations, *Lyon chir.* **26**:834-844 (Nov.-Dec.) 1929; Evaluation of Early Rising in Abdominal Surgery After Four Years, *ibid.* **30**:122 (Jan.-Feb.) 1933.

6. Violet, H.: On the Subject of Early Rising for Operated Patients, *Avenir méd.* **29**:247-250 (Sept.-Oct.) 1932.

7. Villard: Two Cases of Fatal Embolism During the Course of Early Rising After Operation, *Lyon chir.* **30**:606-608 (Sept.-Oct.) 1933.

8. Chaliér, in discussion on Villard.⁷

9. Zillmer: Favorable Results of Getting Up Shortly After an Appendectomy, *Veröffentl. a. d. Geb. d. Heeres-San.-Wes.*, 1930, no. 84, pp. 127-138.

10. Charbonnier, A.: Early Rising After Operation, with Report of One Hundred and Twelve Cases, *Rev. méd. de la Suisse Rom.* **55**:402-466 (June 25) 1935.

11. Gullotta, G.: Early Rising for Operated Patients, *Minerva med.* **26**:322-325 (March 10) 1935.

12. Coniglio, G.: Concerning the Early Rising of Operated Patients, *Riv. san. siciliana* **23**:120-122 (Jan. 15) 1935.

13. Salishchev, V. E., and Ayziks, I. G.: Active Postoperative Regime (Early Rising), *Novy khir. arkhiv.* **36**:260-277, 1936.

14. Florcken, H.: Getting Up Following Surgical Operations, *Munchen. med. Wchnschr.* **83**:917 (June 5) 1936.

15. Ricci, G.: Concerning Immediate Rising of Patients Who Have Undergone Operation, *An. de cir.* **2**:175-207 (Aug.) 1936.

were Folliasson,¹⁶ Polichetti,¹⁷ Pierre Smith,¹⁸ Daumerie,¹⁹ Wichmann,²⁰ Vincent,²¹ Wohlleben,²² and P. Smith.²³ All were enthusiastic over the rapid recovery and freedom from complications following early rising. Ricard²⁴ had six years' experience with this method without a single case of embolism. Correa²⁵ permitted his patients to be out of bed twelve hours after operation, while Mermingas²⁶ permitted patients to leave the operating room ambulatory after appendectomy under local anesthesia. Harild²⁷ emphasized the relief from the "sickbed feeling" as significant. Mukhina²⁸ reported 527 appendectomies performed during the acute stage of appendicitis; over 50 per cent of his patients were out of bed on the first postoperative day. Kimbarovskiy²⁹ reduced the incidence of pulmonary complications from both gynecologic and gastric operations to approximately one tenth through early rising. He also conducted experimental studies of healing of wounds on dogs in the ambulatory state and dogs forced into a reclining position by means of plaster casts. He³⁰ concluded that in the restricted animal there was a delay in the formation of connective tissue as the result of venous stagnation and a sluggish solution of fibrin. Shaus, Pozhariskiy and Abrikosob³¹ in general expressed agreement with these conclusions. Dell'Oro³² reported 1,569 cases, and Campeanu³³ 3,197 cases without complications. Zava³⁴ stated that among 6,000 patients out of bed on the first postoperative day there was not a single case of embolism or eventration. No special technic was employed.

The enthusiasm expressed by these authors is impressive. They reported that in over 15,000 patients subjected to early rising only 4 fatal emboli developed and at least 1 of these was questionable.

16. Folliasson, A.: Early Rising in Abdominal Surgery, *Bull. et mém. Soc. nat. de chir.* **59**:1121-1127 (July 15) 1933.

17. Polichetti, E.: Early Rising After Laparotomy, *Gazz. d. osp.* **54**:1337-1340 (Oct. 22) 1933.

18. Smith, P.: Early Rising in Abdominal Surgery, *Paris méd.* **2**:68-73 (July 21) 1934.

19. Daumerie, L.: Concerning Early Rising After Operation, *Bruxelles-méd.* **18**:534-547 (Feb. 20) 1938.

20. Wichmann, S. E.: Concerning the Significance of "Early Rising" in the Prophylaxis of Thrombosis and Embolism, *Acta Soc. med. fenn. duodecim* (Ser. B., fasc. 1-2, art. 2) **27**:1-11, 1939.

21. Vincent, G.: Early Rising in Abdominal Surgery, *J. de méd. de Paris* **56**:252-253 (Sept. 24) 1936.

22. Wohlleben, T.: Early Rising After Operations, *Arch. f. klin. Chir.* **189**:382-385, 1937.

23. Smith, P.: Early Rising in Abdominal and Pelvic Surgery, *Union méd. du Canada* **69**:921 (Sept.) 1940.

24. Ricard: Embolism and Early Rising, *Lyon chir.* **36**:448 (July-Aug.) 1939.

25. Correa, B.: Immediate or Early Rising: One Hundred and Thirty-Eight Cases, *Rev. brasil. de med. e farm.* **12**:3-11, 1936; *Lyon chir.* **34**:37-48 (Jan.-Feb.) 1937.

26. Mermingas, K.: Early Rising After Operation, *Zentralbl. f. Chir.* **50**:2424-2425 (Sept. 27) 1930.

27. Harild, S.: Should One Allow Early Getting Up After Laparotomies or Not? *Chirurg.* **12**:703-707 (Dec. 1) 1940.

28. Mukhina, M. V.: Early Rising After Appendectomy in Acute Period, *Vestnik khir.* **40**:231, 1935.

29. Kimbarovskiy, M. A., cited by Khromov.⁴³

30. Kimbarovskiy, M. A.: Experimental Study on the Effect of Early Rising on Healing of Postoperative Wounds, *Novy khir. arkhiv.* **48**:116-121, 1940.

31. Shaus, Pozhariskiy and Abrikosob, cited by Kimbarovskiy.

32. Dell'Oro, B.: The Immediate or Early Ambulatory Therapy After Surgery (Especially Abdominal): Method, Technic and Practical Results in 1,596 Cases, *Rev. méd. de Rosario* **26**:29-49 (Jan.) 1936.

33. Campeanu, L., and Papp, M.: The Importance of Early Rising Following Laparotomy, *Zentralbl. f. Chir.* **27**:1573-1579 (July 3) 1937.

34. Zava, L.: The Advantages of Early Rising After Operations, *Policlinico (sez. prat.)* **47**:865-872 (May 20) 1940.

COMPARATIVE ANALYSIS OF PREVIOUS AND PRESENT SERIES

In a previous publication¹ observations on 383 consecutive appendectomies were reported (cases of rupture excluded), with an average period of confinement to bed of one and five-tenths days. Sixty-six other consecutive surgical procedures, with an average period of confinement to bed of one and nine-tenths days, were also included in the series. There were no pulmonary or circulatory complications and no ill effects from early rising.

The present series of 464 consecutive operations is a continuation of the aforementioned series and consists of 274 appendectomies and 190 other major surgical procedures. Of the patients subjected to appendectomy 39 had chronic and 225

TABLE 1—Average Number of Days of Confinement to Bed and to Hospital After Operation in 464 Cases (Present Series)

Classification of Operations	Total Cases	Days	
		Bed	Hospital
Appendectomy			
Chronic appendicitis	39	1 00	2 59
Acute appendicitis	225	1 00	2 40
Ruptured appendix	10	1 00	9 40
Celiotomy (exploratory)	4	1 00	12 50
Cholecystectomy	25	1 08	7 40
Cholecystotomy	1	1 00	22 00
Choledochostomy	4 *	1 00	6 75
Duodenal diverticulum, removal of	1	1 00	7 00
Gastrectomy, deaths	2 **	1 00	25 00
Gastrectomy, recoveries	1	1 00	10 00
Gastroenterostomy	1	1 00	7 00
Herniorrhaphy, inguinal, indirect (5 bilateral)	34	1 00	6 91
Herniorrhaphy, inguinal, direct (1 bilateral)	8	1 00	7 13
Herniorrhaphy, femoral (1 bilateral)	3	1 00	13 67
Herniorrhaphy, incisional	5	1 00	7 20
Herniorrhaphy, umbilical	4	1 00	4 50
Intestinal adhesions, separation of	1	1 00	4 00
Intestinal resection (obstruction)	1	1 00	17 00
Mastectomy (radical 5, simple 2)	7	1 00	5 29
Pelvic operations (hysterectomy, salpingectomy, oophorectomy, etc.)	33	1 00	6 97
Pelvic operations, tubal pregnancy	5	1 00	5 20
Pelvic operations, with perineal operations	4	1 00	10 00
Perforated duodenal ulcer.	1	1 00	9 00
Perineal operations (interposition, colporrhaphy, etc.)	10	1 00	8 40
Rectal operations	15	1 00	3 93
Renal operations (nephrectomy, lithotomy, etc.)	6	1 00	10 83
Operations on the colon (cancer)	6	1 00	13 00
Thyroidectomy	8	1 75	5 25
Total	464 ***	1 02	4 68

* = 1 death.

acute appendicitis, and in 10 the appendix had ruptured. The average period of confinement to bed after appendectomy was one day, and the average period of post-operative hospitalization for the patients with acute or chronic appendicitis was two and five-tenths days. Patients with ruptured appendixes remained in the hospital for an average of nine and four-tenths days. After other major surgical procedures the average period of confinement to bed was one day, and the average period of hospitalization was seven and three-tenths days³⁵ (For a statistical analysis of the two series, see tables 1 and 2)

All patients were subjected to early rising except 2. One had had a cholecystectomy in which technical difficulties were encountered. (This patient was out of bed

35 Excluding the two deaths (gastric operation)

on the third postoperative day, and recovery was uneventful) For the other, see case 1. For lack of space, minor complications which had no bearing on either the surgical procedure or early rising are not reported in this article, while all other complications are mentioned in case reports. (By early rising I now mean that the patient is to be out of bed by the first postoperative day, and only in rare instances by the second.)

It was necessary to rehospitalize 3 patients shortly after dismissal from the hospital. One, who left the hospital on the second day after a simple appendectomy, suddenly became ill with abdominal pain, chills and fever on the seventh day, after

TABLE 2—Average Number of Days of Confinement to Bed and to Hospital After Operation in 900 Cases (Present and Previous Series)

Classification of Operations	Total Cases	Days	
		Bed	Hospital
Appendectomy			
Chronic appendicitis	147	14	25
Acute appendicitis	487	12	23
Ruptured appendix	10	10	94
Celiotomy (exploratory)	7 *	10	99
Cholecystectomy ..	43	13	78
Cholecystotomy ..	3	17	247
Choledochostomy . .	4 *	10	68
Duodenal diverticulum, removal of.	1	10	70
Gastrectomy, recoveries	3	13	107
Gastrectomy, deaths .	2 **	10	250
Gastroenterostomy .	3	13	87
Herniorrhaphy, inguinal, indirect (5 bilateral)	41	11	68
Herniorrhaphy, inguinal, direct (1 bilateral)	10	12	70
Herniorrhaphy, femoral (1 bilateral).	3	10	137
Herniorrhaphy, incisional.... .	5	10	72
Herniorrhaphy, umbilical. .	4	10	45
Intestinal adhesions, separation of. ..	3	10	77
Intestinal resection (obstruction)	1	10	170
Marsupialization of pancreatic cyst .	1	50	300
Mastectomy (radical 5, simple 2) .	7	10	53
Pelvic operations (hysterectomy, salpingectomy, oophorectomy, etc)	49	14	74
Pelvic operations, tubal pregnancy... .	5	10	52
Pelvic operations, with perineal operations .	4	10	100
Perforated duodenal ulcer	1	10	90
Perineal operations (interposition, colporrhaphy, etc)	10	10	84
Prostatectomy. ..	1	20	180
Rectal operations	15	10	39
Renal operations (nephrectomy, lithotomy, etc)	7	14	106
Splenectomy	2	20	85
Operations on the colon (cancer) .	6	10	130
Thyroidectomy ..	15	18	56
Total	900 ****	13	40

* = 1 death

recovery appeared complete. Since the complication, a peritoneal infection, occurred so late, suspicion was placed on the catgut. However, the condition completely subsided without surgical intervention. The second patient had undergone removal of a ruptured appendix. The wound was treated with sulfanilamide applied intra-peritoneally and was closed without drainage. The patient was out of bed on the first postoperative day, and ambulation was gradually instituted. On the seventh day the patient appeared well and was permitted to leave the hospital. A few days later a cul-de-sac abscess developed, and the patient was rehospitalized for drainage (five days). The usual daily out of bed exercises were employed; there were no sequelae. For the history of the third patient see case 7.

Only 4 infections of wounds occurred, 1 after appendectomy and 1 each after femoral, incisional and inguinal herniorrhaphy. The 2 infections following incisional and inguinal herniorrhaphy developed in wounds closed with nylon sutures. Drainage was prolonged, and both patients were later rehospitalized at another institution. My experience with nylon was not satisfactory, since granulomas not infrequently occurred as late as ten months after its use. The use of this suture material has been abandoned.

The rapid recovery of patients operated on for appendicitis with rupture may be attributed to control of the infection with sulfanilamide applied intraperitoneally, to closing the abdomen without drainage and to early rising to avoid further complications. A small extraperitoneal drain was always employed.

There were 3 deaths in this series. One occurred before early rising was instituted.

CASE 1.—Mr. A. B., aged 66, suffered a coronary attack and died suddenly six hours after a cholecystectomy and choledochostomy performed for obstructive jaundice with a septic temperature and cardiac irregularity.

The other 2 patients who died were subjected to early rising and respiratory exercises. Improvement was significant before the terminal stage.

CASE 2.—Mr. J. V., aged 59, died on the fifteenth day after a palliative gastrectomy performed for carcinoma with extension to the pancreas. The patient was out of bed several times daily beginning on the first postoperative day. There was some moisture in the lungs (palpable rales) for the first two days. Coughing exercises in the standing position readily expelled the mucous plugs, with permanent relief by the second day. There was no distention; there was a bowel evacuation on the fifth day and diet was instituted on the sixth. On the eighth day pain developed in the upper right quadrant of the abdomen; this was followed by a subhepatic abscess; the patient was then confined to bed until death.

CASE 3.—Mr. E. D., aged 59, died on the thirty-sixth day after a partial gastrectomy performed in the presence of cholangitis. (The preoperative diagnosis was biliary disease.) Exploration revealed a chronic perforated gastric ulcer walled off by the pancreas (not visualized by roentgen rays). Accidental rupture of the ulcer demanded gastric resection. The patient was out of bed several times daily for respiratory exercises, occasionally taking a few paces. There was some moisture in the lungs (palpable rales) for several days. Coughing exercises in the standing position readily expelled the mucous plugs. He was never able to take food. Atresia of the stoma was anticipated, and distress was controlled by Wangenstein suction. He was not constantly confined to bed until the twenty-third day. Death was due to hepatitis and inanition.

In the following 2 cases the pulmonary complications, which were the gravest in the entire series, were readily controlled. The elimination of moisture from the lungs through coughing exercises in the standing position is noteworthy.

CASE 4.—Mrs. A. S., aged 58, unusually obese, was critically ill for eleven days with empyema of the gallbladder. She had a septic temperature of 104 F., and a pulse rate of 120 before surgical intervention. The upper right quadrant of the abdomen was a solid mass of inflammation. The gallbladder was perforated but walled off by the duodenum and colon and contained thick pus and stones, which were removed. Chemotherapy was applied and drainage instituted. The following day there was intermittent muttering delirium, and rales could be heard outside the room; the patient appeared beyond hope. Coughing in the standing position recovered an enormous amount of thick, purulent mucus. Although the patient could scarcely stand with support, the relief was so gratifying that she requested these exercises repeated as rales recurred; this was several times daily. The lungs remained clear after the third day, and ambulation was instituted. On the seventh day meals were served out of bed; there was a normal bowel evacuation on the eighth day. On the twenty-second day she left the hospital by automobile in excellent condition.

CASE 5.—Mr. L. F., aged 54, was out of bed for respiratory exercises on the first day after a cholecystectomy; the lungs were relatively clear. On the second day a type VII lobar pneumonia developed in the right lung. Specific serum was administered, and chemotherapy was instituted. Coughing exercises in the standing position recovered large amounts of rusty

sputum. These exercises were repeated several times daily. By the fourth day the temperature and pulse remained normal, and ambulation was instituted. By the seventh day the patient felt well and wanted to go home; permission was granted on the ninth day. There were no sequelae.

There was 1 case of dehiscence, associated with pronounced avitaminosis, and not to be charged to early rising.

CASE 6.—Mr. W. M., aged 41, had annular carcinoma of the sigmoid flexure, diagnosed preoperatively by means of a roentgenogram. Exploratory laparotomy through a left rectus incision revealed pronounced distention and engorgement of the descending colon from the splenic flexure to the anus. Extensive rales were present on the following day; the mucus was eliminated by coughing exercises in the standing position. In spite of periodic hallucinations, ambulation was instituted. The distention could not be controlled, a difficulty encountered before operation. On the fifth day it was disclosed that the patient had chronic alcoholism, and that a pyorrhea of weeks' standing had developed into a pronounced generalized stomatitis suggesting a deficiency of the vitamin B complex. Examination revealed dehiscence of the fascial layers. Thereafter he was confined to bed, and the distention and pyorrhea rapidly disappeared when vitamin therapy was employed. An incisional hernia was to be expected.

There was 1 case of thrombophlebitis, the reflex value of which was relieved by injecting procaine hydrochloride into the paravertebral ganglions.

CASE 7.—Mrs. M. B., aged 51, acutely ill with biliary jaundice, chills and fever (102 F.), was subjected to cholecystectomy and choledochostomy for stones and cholangitis. She was out of bed on the first postoperative day. Her chest was clear, and ambulation was gradually instituted. Improvement was rapid, and she left the hospital on the eleventh day. Two days later thrombophlebitis of the left leg suddenly developed. Her temperature was 103 F. and her pulse rate 120. She was rehospitalized. On three consecutive days procaine hydrochloride was injected into the left paravertebral ganglions to block the reflex arc; relief from pain was prompt. The patient was ambulatory after the first day. Her temperature and pulse remained normal after the sixth day, and she was discharged on the twelfth day. Some swelling of the leg was still present two months later.

In a series of 70 herniorrhaphies (46 indirect, 11 direct, 4 femoral, 4 umbilical and 5 incisional), 7 of which were bilateral, there have been 4 recurrences of inguinal hernia and 1 of incisional hernia.

The patients in this series were not from a clinic but private patients with whom I have had almost constant contact. Recently a questionnaire was compiled covering both series, with the following questions: "Did you feel better or worse following early rising?" Over 98 per cent replied favorably; the complaints of the remainder had no bearing whatever on early rising and observation revealed no ill effects in any instance.

SURGICAL TECHNIC AND SUTURES

Spinal anesthesia was routinely employed, and recently the Lemmon technic for fractional spinal anesthesia has been used for the more prolonged operations.

All appendical incisions were of the muscle-splitting type located just external to the linea semilunaris, the rectus sheath being split only when necessary. All incisions for operations on the biliary tract were oblique, bordering on the transverse, just below the costal arch. All incisions for gastric and pelvic operations were midline. There was but 1 midrectus incision (case 6). (Midrectus incisions are not desirable, since sutures in the transversalis fascia are parallel to its fibers.)

All appendical incisions were closed with interrupted single strand 000 chromic catgut.³⁶ All other incisions were closed with a continuous double strand 000 chromic catgut; the anterior layer of fascia was usually reenforced, particularly

36. As has been previously stated, nylon sutures have been discontinued, since not infrequently granulomas developed months after their use.

in the long incisions, with several interrupted double loop sutures of no. 32 alloy steel wire. In some instances, especially when great tension was present or anticipated, the entire closure was accomplished with double loop interrupted sutures of alloy steel wire according to the Jones technic.³⁷ Inguinal hernias were all repaired with wire.

POSTOPERATIVE CARE

After the patient's return from the operating room, 2 fluidounces (60 cc.) of water was administered every two hours for the first twenty-four hours. In the presence of abdominal distention or distress, continuous Wangenstein or Miller-Abbott suction was maintained until the condition was relieved. Electrolyte, water and protein balance were controlled by parenteral routes as indicated. Liquid petrolatum was administered daily, usually beginning on the third post-operative day. Cathartics were never given, and enemas were administered rarely, only if digital examination revealed the necessity. Morphine was liberally administered for pain during the first twenty-four hours. Patients were instructed on the day of operation to take deep breathing exercises and were assisted, if necessary, in changing position every hour.

Technic of Getting Patients out of Bed and Associated Exercises.—The morning after operation patients were requested to assume the right lateral position, with the feet over the edge of the bed, and were assisted to a sitting position. They then stood on a stool beside the bed and were urged to cough. By placing the hand at the bases of the lungs during the coughing exercises, the nurse could readily detect rales, if present, and the rales would invariably be eliminated promptly by the expulsion of the mucous plugs. In the presence of moist lungs the respiratory exercises were repeated several times during the day and were continued daily until the lungs remained clear. Usually one such exercise was all that was required. Only occasionally was it necessary to continue coughing exercises to the third day. Ambulation was gradually instituted, the patient taking only a few paces at the first attempt. For patients with the more serious conditions ambulation was not always instituted during the first out of bed period but usually was well established by the second or third day. More recently daily determinations of vital capacity have been made preoperatively and postoperatively, the significance of which is discussed under the heading of vital capacity.

The time of dismissal from the hospital was governed by the well-being of the patient and his desire to go home. Although many patients in this series had hospital insurance, which those in the previous series did not have, the post-operative stay in the hospital for all patients subjected to major operations has been reduced, while the stay for patients subjected to appendectomy remains practically the same.

Follow-Up of Patients.—On dismissal from the hospital patients were instructed to remain active. Patients would appear at the office on the fifth or sixth day after appendectomy for removal of clips; retention sutures would be removed on the seventh or eighth day. Patients on whom other abdominal operations had been performed usually were seen at the office between the ninth and the twelfth day for care of the wound. In most instances these patients were permitted to return to work in one-half the time usually prescribed.

37. This consists of a double loop interrupted suture, the first loop through the fascia and peritoneum, the second through the superficial fascia only; before the ends are ligated they are cut short and bent at right angles (Jones, T. E.; Newell, E. T., Jr., and Brubaker, R. E.: Use of Alloy Steel Wire in Closure of Abdominal Wounds, Surg., Gynec. & Obst. 72:1056-1059 [June] 1941).

PATHOLOGIC REFLEXES INITIATE CHANGES THAT
LEAD TO COMPLICATIONS

The local reaction following an abdominal (or other) incision and the removal of the local lesion does not appear to be the important factor in the development of many of the remote complications that not infrequently threaten the life of the patient. When death does take place, autopsy usually reveals many remote pathologic conditions, such as atelectasis, hypostatic pneumonia, intestinal distention, passive congestion and not infrequently venous thrombosis with infarcts in the vital organs. I shall present evidence from the literature that reflexes from the incision and the traumatized areas have a distinct relationship to the development of many of the complications and that early rising and special respiratory exercises lessen the reactions from these reflexes.

Postoperative Vital Capacity in the Recumbent Position.—The reflex inhibition of the diaphragm, in which the diaphragm assumes a high position and limited excursion after an abdominal operation, and which in turn results in a pronounced diminution in vital capacity and tidal air, is recognized. Patey³⁸ demonstrated this diaphragmatic inhibition by means of the roentgen rays, while extensive studies have been made of vital capacity (on patients in the recumbent position) before and after surgical procedures, at the Massachusetts General Hospital by Churchill and McNeil³⁹ and later by Powers,⁴⁰ Beecher⁴¹ and Cutler and Hoerr.⁴² From their observations it is established that immediately after a surgical procedure on the abdomen there is a pronounced diminution in vital capacity, most evident on the first postoperative day, after which the vital capacity gradually improves, reaching normal usually between the seventh and the fourteenth day (broken lines, charts 1 and 2). The extent and duration of the reduction in vital capacity bear a direct relation to the extent of the surgical procedure. It has been emphasized by Patey³⁸ and Beecher⁴¹ that the tidal air is diminished in direct ratio to the reduction in vital capacity, which course the tidal air follows in returning to normal. Churchill and McNeil,³⁹ Beecher,⁴¹ Cutler and Hoerr,⁴² Khromov⁴³ and others emphasized that pulmonary complications increase in direct proportion to the reduction and duration of reduction of vital capacity, while Cutler and Hoerr stated that 50 per cent of all primary postoperative pulmonary complications are established by the end of twenty-four hours and that 90 per cent make their appearance before the end of the fourth day. Incidentally, the presence of pulmonary complications causes a secondary drop in vital capacity, which remains below the normal postoperative level until the complication subsides. The remote systemic changes which may occur as a result of this crippled respiration can be appreciated. Attempts have been made to overcome the reduction of postoperative vital capacity with the hope of decreasing the incidence of pulmonary and other complications. These attempts have not met with any material success.

38. Patey, D. H.: The Effect of Abdominal Operations on the Mechanism of Respiration, with Special Reference to Pulmonary Embolism and Massive Collapse of the Lungs, *Brit. J. Surg.* **17**:487-497 (Jan.) 1930.

39. Churchill, E. D., and McNeil, D.: The Reduction in Vital Capacity Following Operation, *Surg., Gynec. & Obst.* **44**:483-488 (April, pt. 1) 1927.

40. Powers, J. H.: Vital Capacity: Its Significance in Relation to Postoperative Pulmonary Complications, *Arch. Surg.* **17**:304-323 (Aug.) 1928.

41. Beecher, H. K.: Measured Effect of Laparotomy on Respiration, *J. Clin. Investigation* **12**:639-650 (July) 1933.

42. Cutler, E. C., and Hoerr, S. O.: Postoperative Pulmonary Complications, *Proc. Interst. Postgrad. M. A. North America* (1941), 1942, pp. 232-237.

43. Khromov, B. M.: Value of Early Rising After Operation in Prevention of Postoperative Pulmonary Complications, *Sovet khir.*, 1936, no. 9, pp. 389-397.

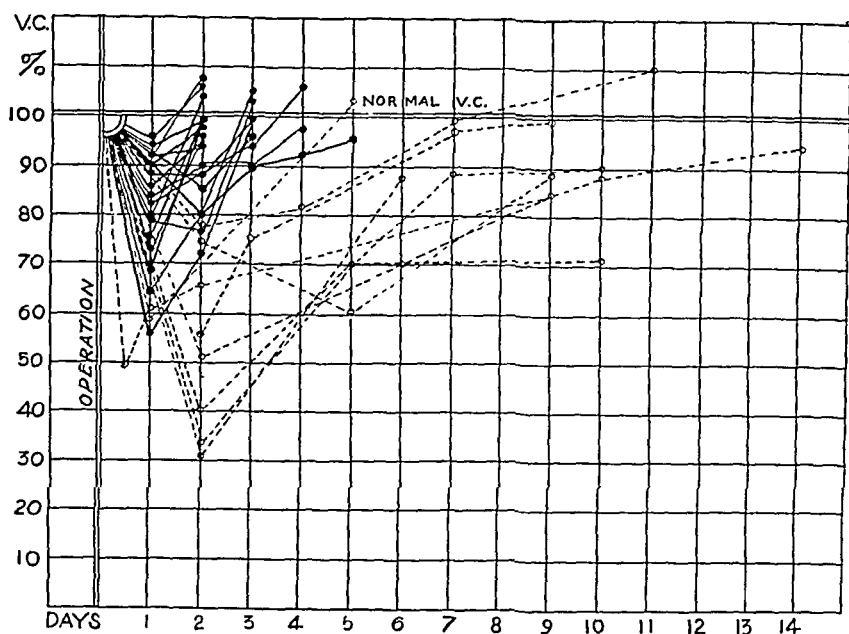


Chart 1.—Heavy lines represent course of vital capacity (daily values) in patients subjected to early rising after appendectomy. Broken lines represent comparable data compiled by Churchill and McNeil³⁹ for patients not subjected to early rising. (A muscle-splitting incision was used in both series.)

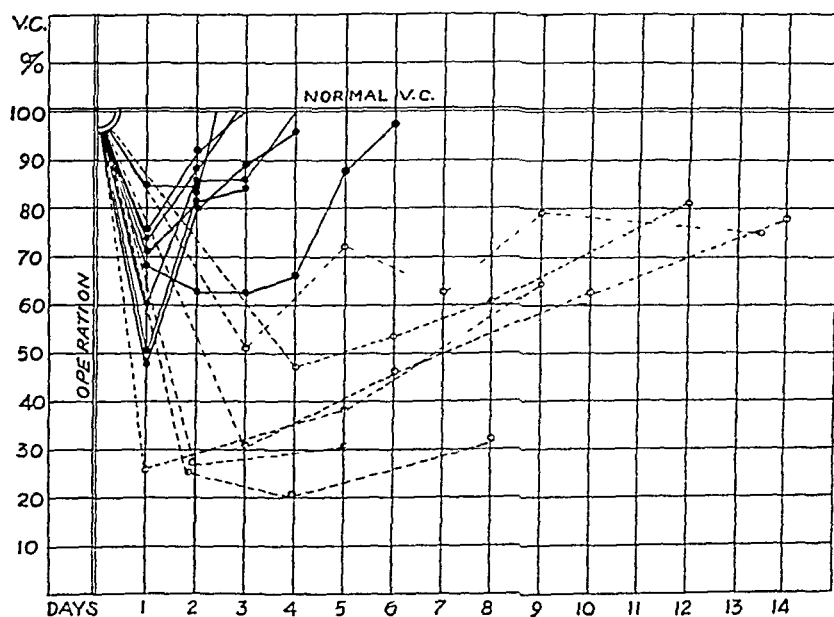


Chart 2.—Heavy lines represent course of vital capacity (daily values) in patients subjected to early rising after operations on the biliary tract (transverse incision). Broken lines represent comparable data compiled by Churchill and McNeil³⁹ for patients not subjected to early rising (vertical rectus incision).

The Effect of Early Rising on Crippled Respiration.—Readings of vital capacity were made each day for 202 patients subjected to early rising, in the lying, sitting and standing positions before and after surgical procedures on the abdomen. For accuracy, at least three determinations were made in each position. The McKesson-Scott spirometer was employed because of its simplicity of operation. In the final analysis only the vital capacity in the standing position was considered, since there was no material difference in any position. After early rising the vital capacity returned to normal much sooner, usually in less than one-half the prescribed period; convalescence closely followed the improvement in vital capacity. Graphs representing changes in vital capacity following early rising are presented for comparison with Churchill and McNeil's graphs of patients not subjected to early rising. Study of these graphs and the following case reports corroborate these findings (charts 1 and 2).

It was recognized early in these studies that coughing exercises in the standing position would augment rales that could be readily palpated at the base of the lungs—rales which were usually not considered significant or were not detectable when the patient was in the recumbent position. This, I believe, was due to the high, inhibited diaphragm, which in the standing position would be lowered by the downward pull of the abdominal contents, thus opening the collapsed tubules and permitting air to enter. The fact that mucous plugs would then be promptly expelled by coughing (coughing not infrequently automatically induced) supports this contention. Prompt disappearance of rales on expulsion of the mucous plugs by coughing is a specific therapy and a pathognomonic sign of incipient post-operative atelectasis.

Vital Capacity in Early Rising.—The following case reports show a rapid return of vital capacity to normal is a result of early rising. Also note that the course of convalescence was parallel to this curve. This was a characteristic feature in this series.

CASE 8.—Mrs. G. P., aged 35, three months pregnant, was suffering with biliary colic. A cholecystectomy was performed for cholelithiasis. She was ambulatory several times on the first postoperative day, and ambulation was increased daily thereafter. Vital capacity before operation was 3.0 liters. Vital capacity on each of the first five postoperative days was as follows: 1.8, 2.6, 2.6, 3.0 and 3.0 liters. The patient asked to leave the hospital on the fifth day; permission was given on the sixth day. She remained active, and no further medical attention was required except removal of retention sutures. She gave birth to twins at term.

CASE 9.—Mrs. M. R., aged 37, weighing 287 pounds (130 Kg.), had a cholecystectomy performed for biliary colic. She was ambulatory several times on the first postoperative day, and her lungs were clear. Ambulation was increased daily as tolerated, and by the fourth day she was especially active, even climbing stairs. Vital capacity before operation was 2.6 liters. Daily vital capacity for the first seven days after operation was as follows: 2.0, 2.4, 2.6, 2.6, 2.8, 2.9 and 2.8 liters. The patient asked to leave the hospital on the fifth day, and permission was granted on the seventh day. Retention sutures were removed on the tenth day.

CASE 10.—Mr. H. G., aged 30, was subjected to partial gastrectomy for cancer. On the first postoperative day there was incipient atelectasis. Loud rasping rales were present; the temperature was 104 F. and the pulse rate 120. Coughing in the standing position raised large amounts of thick, purulent mucus. The exercises were repeated several times on this day, and by the second day the lungs remained clear. Ambulation began on the third day and increased daily thereafter. On the fifth day the temperature, pulse and function of the bowels were normal. The patient left bed frequently, unaided. On the eighth day he asked to leave the hospital. Permission was granted on the tenth day, and he returned to work on the thirteenth day. There were no sequelae. Vital capacity before operation was 6 liters. On the first ten postoperative days it was 2.0, 3.5, 4.3, 4.0, 4.8, 4.8, 5.8, 5.8, 6.0 and 6.0 liters respectively.

CASE 11.—Mr. J. L., aged 47, was operated on for the removal of a diverticulum 5 by 3 by 3 cm. on the outer and posterior surface of the duodenum. The appendix was also

removed. On the first postoperative day extensive palpable rales were present at the bases of both lungs. On coughing in the standing position the mucous plugs were expelled, and ambulation was instituted. By the third day the lungs remained clear. The vital capacity before operation was 5.0. On the first eight postoperative days it was 3.2, 3.8, 4.2, 4.5, 4.7, 5.0, 5.0 and 5.0 liters respectively. He asked to leave the hospital on the sixth day; permission was granted on the eighth day; office care was given on the tenth day.

CASE 12.—Mr. G. G., aged 82, had a gastroenterostomy performed for pyloric obstruction incident to ulcer. He was out of bed on the first postoperative day for respiratory exercises and was ambulatory thereafter. Rales were present the first day, and the patient had auricular fibrillation for three days. There was no urinary retention, and the bowels functioned normally. The vital capacity before operation was 3.4 liters. On the first seven postoperative days it was 3.1, 3.0, 3.0, 2.8, 3.8, 3.8 and 3.8 liters respectively. The patient was dismissed on the seventh day in excellent condition.

CASE 13.—Mr. E. S., aged 16, had acute appendicitis, with a white cell count of 18,500. He was ambulatory the day after appendectomy; his lungs were clear. The preoperative vital capacity was 4.6 liters, and on the first postoperative day the capacity was 4.4 liters. He felt well and left the hospital that afternoon. He had a normal bowel movement the following day and attended the theater in the evening. After the third postoperative day he clerked in a store. Clips were removed on the sixth day.

Note the low preoperative vital capacity due to peritonitis in the following case report.

CASE 14.—Mr. J. B., aged 16, was subjected to appendectomy for rupture of a gangrenous appendix with rapidly spreading peritonitis. His temperature was 102 F. and his pulse rate 144. One hundred and twenty grains (7.75 Gm.) of sulfanilamide was placed in the peritoneal cavity and wound. Suction with a Miller-Abbott tube, parenteral administration of fluids and transfusion of plasma were employed. There were periods of delirium. The patient stood beside the bed several times each day for breathing exercises and was ambulatory on the third day. The vital capacity before operation was 1.0 liter. On the first twelve days after operation it was 2.0, 2.2, 2.1, 2.0, 2.2, 2.2, 2.1, 2.4, 2.4, 2.4, 2.6 and 3.0 liters respectively. Normal bowel evacuation occurred on the third day. The patient left the hospital ambulatory on the twelfth day and was given office care thereafter.

Effect of Reflexes on the Vascular Bed and Functional Activity of Vital Organs.—Postoperative thrombophlebitis of the lower extremities, which so frequently is followed by pulmonary embolism, is considered, at least in part, a reflex phenomenon. By breaking the reflex arc early through the injection of procaine hydrochloride into the paravertebral ganglions, invariably prompt relief is obtained⁴⁴ (see case 7). These reflex vascular and functional changes following surgical procedures are not necessarily confined to the lower extremities. It is probable that the vital organs not infrequently are so affected, with or without clinical evidence. For instance, suppression of renal and hepatic function and abdominal distention are common occurrences following the more serious surgical procedures. Pathologic reflexes, to the diaphragm, to the vascular bed and to the vital organs, appear immediately after an incision is made. These reflexes depress respiration, circulation and organic function, thereby promoting anoxia, incomplete metabolism and faulty elimination. Morbidity and complications mount with the intensity and prolongation of these reflexes. Stimulation of respiration and circulation through early rising, deep breathing and coughing exercises, followed by ambulatory activity, is the most effective means of lessening the reactions due to these reflexes and of hastening recovery.

SUMMARY AND CONCLUSIONS

There are several important postoperative reflexes originating from wounds and traumatized areas which initiate pathologic changes leading to complications.

44. Ochsner, A.: Treatment of Thrombophlebitis by Novocain Block of Sympathetics: Technique of Injection, *Surgery* 5:491-497 (April) 1939.

The effect of the reflex to the diaphragm can be measured and expressed in the percentage of reduction of vital capacity. In some instances the reduction is over 60 per cent on the first postoperative day, and seven to fourteen days is usually required for vital capacity to return to normal. Pulmonary complications increase in direct proportion to the reduction in vital capacity. Fifty per cent of pulmonary complications are established in twenty-four hours and 90 per cent appear by the fourth day.

In the presence of pulmonary complications coughing in the standing position, if instituted during the first twenty-four hour period (when the vital capacity is at its lowest level), will invariably promptly expel the mucus and cause prompt disappearance of the rales. Repetition of the exercises as occasion demands will invariably maintain clear lung fields.

Coughing in the standing position is particularly effective, since the downward pull of the abdominal contents lowers the diaphragm, permitting air to enter the collapsed tubules beyond the mucous plugs. The lowering of the diaphragm appears to be the explanation why the vital capacity returns to normal so rapidly (in two to seven days) when early rising is instituted.

The curve of postoperative vital capacity is also an index of the stage of convalescence. Recovery after an abdominal operation improves with the improvement of this curve. This is graphically demonstrated in this article by comparable vital capacity curves and case reports. These comparisons emphasize the importance of instituting early rising at the low level of the vital capacity within the first twenty-four hour period. From the literature and my recent observations, I believe the most effective time to be immediately after recovery from the anesthetic.

The effect of early rising on other reflex changes, such as inhibition of the vital organs and reflex vascular changes that lead to thrombosis, has been emphasized.

Deliscence, incisional hernias and recurrences following inguinal herniorrhaphies were not more frequent after early rising. There was no instance of eventration in the 900 cases. The tensile strength of sutures is greater during the early postoperative period, and healing is promoted through ambulatory activity, as Kimbarovskiy²⁹ and others have demonstrated. Thus the incision of the patient who rises early should stand the strain more readily than that of the patient who rises at some later date. So far as deliscence and eventration are concerned, the most dangerous time to get up is between the fifth and the tenth day, the lag period in healing which is not present when early rising is employed.

Limiting confinement to bed to twenty-four hours relieves postoperative distress and rapidly restores the patient to health and to ability to work. This should be of tremendous value during the present emergency, especially to the armed forces, for whom rapid recovery and mobility are so essential.

This practice can be applied to all surgical procedures mentioned in this article in practically all instances, providing the type of incision is well chosen and the wound is properly closed with well selected suture material.

The chief obstacle to early rising is fear and respect for tradition on the part of the surgeon and the patient. Pain and discomfort are insignificant. Even the neurotic or fearful patient, who thinks he is too sick to move, is enthusiastic about early rising once it is established. A common explanation for the presence of complications is, "He got up too soon"; but in reality he got up too late.

Drs. E. D. Churchill and D. McNeil gave permission to copy their graphs on vital capacity. Miss Theresa Aceti carried out the determinations of vital capacity reported in this article. Dr. A. J. Carlson reviewed the entire study and offered criticism and comment.

CEILING OF UTILIZATION OF NITROGEN

EFFECT OF CONTINUOUS VENOCLYSIS WITH THE AMINO ACIDS OF HYDROLYZED PROTEIN DURING EXPERIMENTAL HYPOALBUMINEMIA

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The correction of protein deficiencies of nutritional origin is a serious quantitative problem whenever the depletion is so severe as to require a large amount of protein alimentation. If but a short time is available for correction, the difficulties are multiplied. Moreover, in many cases the parenteral route must be used. The purpose of the study reported here was to determine if possible the ceiling of utilization of intravenously given amino acids and polypeptides, i. e., how rapidly protein depletions can be corrected. An analogy may be drawn between this problem and that of vitamin deficiencies, many of which may often be corrected completely within a few hours or days by giving sufficiently large amounts of vitamins.

As far as could be determined, no previous observations have been made with intravenous injections of really large doses of mixtures of amino acids. In the St. Louis City Hospital as much as 300 Gm. of hydrolyzed casein daily for three days has been so administered to 2 patients without difficulty.¹ In a study by Brunschwig, Clark and Corbin² the greatest amount of the same hydrolysate injected in one day was 150 Gm. for ten consecutive days for a patient weighing 50 Kg.

METHODS

Mongrel dogs were depleted according to the method previously described³ by putting them on an almost nitrogen-free diet containing a mixture of corn syrup (Karo), Ringer's solution and a vitamin B complex concentrate. Treatment was started after three weeks of this regimen, when hypoalbuminemia was present. A continuous intravenous injection was carried out with the animals suspended in a Pavlov frame. In all cases the total amount of hydrolyzed protein injected was the same as in previous experiments during a week-long period of therapy, i. e., 3.5 Gm. of nitrogen per kilogram of body weight. Urine was collected for the last six or seven days of the depletion period, and during and for six or seven days following venoclysis.

Three experiments were performed, each on 2 dogs as follows:

Experiment 1. The stated amount of hydrolyzed protein as a 10 per cent solution was injected continuously during the course of twenty-four hours. The total volume was 280 cc. per kilogram of body weight. The results are summarized in table 1.

From the Department of Surgery, Washington University and Barnes Hospital.

1. Elman, R.; Weiner, D. O., and Bradley, E.: *Ann. Surg.* **115**:1165, 1942.

2. Brunschwig, A.; Clark, D. E., and Corbin, N.: *Ann. Surg.* **115**:1091, 1942.

3. Sachar, L. A.; Horwitz, A., and Elman, R.: *J. Exper. Med.* **75**:453, 1942.

Experiment 2. In this experiment an equivalent amount of dextrose was added, i. e., a solution containing 5 per cent of the hydrolysate and 5 per cent of dextrose was used. This, of course, doubled the volume of the injected fluid, which was 560 cc. per kilogram of body weight. The results are summarized in table 2.

Experiment 3. In this experiment the continuous venoclysis lasted forty-eight hours instead of twenty-four hours, the daily dose of hydrolysate therefore being one half as large, i. e., 1.75 Gm. of nitrogen per kilogram of body weight. Dextrose was added to the solution, which as made up contained 7.5 per cent of the hydrolysate and 2.5 per cent of dextrose. The total volume injected was 375 cc. per kilogram of body weight. The results are summarized in table 3.

The hydrolyzed protein used was a mixture of amino acids and polypeptides obtained by the enzymic hydrolysis of casein and pork pancreas.⁴ During the period of intravenous injections, the usual gavage feedings were omitted.

The chemical methods are the same as those described in previous papers⁵; the plasma volumes were determined by the method as already described.^{5a} In estimating the amino acid nitrogen of the urine the method of Sahyun was used.⁶

EXPERIMENTAL OBSERVATIONS

The intravenous injections were tolerated well in all cases; the rate of flow did not in any instance produce vomiting. However, if the rate was not maintained uniformly and the injected fluid flowed much more rapidly even for a period of ten or fifteen minutes, salivation did occur. In only 1 instance was the animal sufficiently restless to require the use of a barbiturate. The intravenous flow produced no particular difficulties except that the needle in most cases had to be changed from time to time from one leg to another because of obstruction to the flow, and a transient edema of the injected limb was often observed.

The data listed in tables 1, 2 and 3 reveal increases in serum protein concentration after the injections in all three experiments. Positive nitrogen balance was also achieved during the period of the injections. However, with the twenty-four hour injections (experiments 1 and 2) there was a pouring out of extra nitrogen in the days after the cessation of the intravenous therapy. Moreover, the increase in the concentration of albumin in these experiments was transient. Indeed by the end of the week after the twenty-four hour injections the concentration of albumin had fallen to a level even lower than when treatment was begun, a circumstance which suggests that little if any of the injected material remained as serum protein. That the actual increase was due to hemoconcentration rather than regeneration was indicated by increases both in globulin and in hematocrit value. A similar outpouring of nitrogen in the period after the injection of large amounts of plasma was also observed in previous experiments in this laboratory.^{5b}

An important finding was the large amount of amino acids in the urine of one of the dogs in experiment 1. Of the 12 Gm. of nitrogen excreted in the urine during the period of injection, nearly 3 Gm. was present as amino acids. This excessive amount indicates that during rapid injection amino acids are actually spilled in the urine. That the absence of dextrose in the injected fluid was partly responsible is shown by the fact that no such amounts were found in the urine in

4. The trade name of this product is Amigen, and it was furnished by Mead Johnson and Company of Evansville, Ind.

5. (a) Elman, R.; Brown, F. A., Jr., and Wolff, H.: *J. Exper. Med.* **75**:461, 1942. (b) Elman, R., and Davey, H. W.: *ibid.* **77**:1, 1943. (c) Sachar, Horwitz and Elman.²

6. Sahyun, M.: *J. Lab. & Clin. Med.* **24**:548, 1939.

TABLE 1.—*Regeneration of Plasma Albumin and Nitrogen Balance Following a Twenty-Four Hour Venoclysis with a 10 Per cent Solution of a Casein Hydrolysate*

Days	Body Weight, Kg.	Hematocrit Value, %	Plasma Albumin, Gm. per 100 Cc.	Plasma Globulin, Gm. per 100 Cc.	Plasma Volume (Dye Method), Cc.	Total Albumin, Gm.	Nitrogen Intake, Gm.	Nitrogen Output in Urine, Gm.
Dog 1								
1	6.7	41.4	2.77	3.35	0.07	
14	...	36.9	1.81	3.19	0.07	
20	6.6	32.8	1.47	2.90	466	5.97	0.42 (6 days)	6.45 (6 days)
21	...	35.2	2.05	4.01	428	8.77	24.04 (1 day)	12.92* (1 day)
22	...	31.0	1.61	3.26	0.07	5.50
23	0.07	2.12
24	0.07	1.25
25	0.07	0.65
26	0.07	1.60
27	...	27.4	1.42	3.29	0.07	0.60
								11.72 (6 days)
Dog 2								
1	11.8	46.3	4.01	2.95	0.07	
14	...	34.4	2.58	2.52	0.07	
20	10.2	34.7	2.69	2.57	558	15.0	0.42 (6 days)	8.85 (6 days)
21	...	36.1	3.18	2.99	549	17.5	36.04	†
22	...	28.6	2.63	2.30	0.07	4.53
23	0.07	1.96
24	0.07	1.91
25	0.07	0.93
26	0.07	1.24
27	...	31.8	2.44	2.11	0.07	0.91
								11.53 (6 days)

* Amino acid nitrogen, 2.81 Gm.

† Specimen incomplete.

TABLE 2.—*Regeneration of Plasma Albumin and Nitrogen Balance Following a Twenty-Four Hour Venoclysis with a Solution Containing 5 Per Cent of a Casein Hydrolysate and 5 Per Cent of Dextrose*

Days	Body Weight, Kg.	Hematocrit Value, %	Plasma Albumin, Gm. per 100 Cc.	Plasma Globulin, Gm. per 100 Cc.	Nitrogen Intake, Gm.	Nitrogen Output in Urine, Gm.
Dog 3						
1	7.8	40.8	3.04	3.01	0.10	
14	7.2	47.2	2.91	3.65	0.10	
20	6.6	36.1	2.49	3.01	0.60 (6 days)	9.82 (6 days)
21 (a. m.)	...	53.6*	3.19	3.67	22.70 (1 day)	9.15 (1 day)
(p. m.)	...	46.2	2.79	3.42	...	amino acid N = 0.84 Gm.
22	...	41.8	2.44	3.10	0	4.12
23	0.10	3.13
24	0.10	2.39
25	0.10	1.99
26	0.10	0.72
27	...	33.6	2.29	3.02	0.10	0.61
					0.50 (6 days)	12.93 (6 days)
Dog 4						
1	11.8	52.3	4.66	2.53	0.16	
14	10.6	52.8	3.61	2.38	0.16	
20	11.0	53.7	3.43	2.58	0.96	15.96 (6 days)
21 (a. m.)	...	61.6*	3.84	2.92	37.84	10.84 (1 day)
(p. m.)	...	55.8	3.51	2.84	...	amino acid N = 0.85 Gm.
22	...	49.5	3.39	2.75	0	7.79
23	0.16	5.46
24	0.16	5.74
25	0.16	1.56
26	0.16	2.01
27	...	37.4	2.89	2.00	0.16	1.69
					0.80 (6 days)	21.04 (6 days)

* Blood taken two hours after the intravenous injection was completed.

experiment 2. On the other hand, it was surprising that better utilization was not induced by the presence of dextrose in this experiment; perhaps the excessive volume of fluid injected was responsible.

In contrast to the findings with the twenty-four hour injection are the permanent results of the forty-eight hour venoclysis. Here there was good nitrogen balance, which, moreover, was followed by no extra excreting of nitrogen in the week following the injection. The increase in serum albumin was also maintained; moreover, its magnitude was similar to that achieved in the week-long period of therapy already reported.⁷

TABLE 3.—*Regeneration of Plasma Albumin and Nitrogen Balance Following a Forty-Eight Hour Venoclysis with a Solution Containing 7.5 per Cent of a Casein Hydrolysate and 2.5 per Cent of Dextrose*

Days	Body Weight, Kg.	Hemato-crit Value, %	Plasma Albumin, Gm. per 100 Cc.	Plasma Globulin, Gm. per 100 Cc.	Plasma Volume (Dye Method), Cc.	Total Albumin, Gm.	Nitrogen Intake, Gm.	Nitrogen Output in Urine, Gm.
Dog 5								
1	13.0	57.5	4.18	3.14	615	25.7	0.07	
7	12.2	53.7	3.64	2.80	0.07	
14	11.2	54.7	3.51	3.14	0.07	
22	11.4	50.0	2.95	2.76	0.07	11.80 (7 days)
26	11.4	51.5	2.74	2.82	571	15.6	45.60	19.15 (2 days)
28	11.4	47.9	3.14	3.23	606	19.0		
35	10.8	45.0	3.18	3.09	0.07	11.80 (7 days)
Dog 6								
1	9.0	47.1	4.11	2.22	513	21.1	0.07	
7	8.5	51.4	3.64	2.37	0.07	
14	7.6	49.9	3.24	2.55	0.07	
22	8.2	44.6	2.48	2.36	0.07	7.06 (7 days)
26	7.7	41.5	2.60	2.00	404	10.5	31.20	11.6 (2 days)
28	7.6	38.9	2.98	2.56	451	13.4		
35	7.6	37.2	2.98	2.63	0.07	8.63 (7 days)

COMMENT

On the basis of the evidence herein presented, it would seem that the body has a much greater capacity for utilizing intravenously administered amino acids and polypeptides than is generally supposed. Thus, in the present experiments, the daily ceiling for the dog was probably above 1.75 Gm. of nitrogen (11 Gm. of protein) per kilogram of body weight. The practical application of this finding concerns the rapidity with which human protein deficiencies can be corrected. Certainly the usual "1 Gm. of protein per kilogram per day" is small in comparison with the probable capacity of the body to assimilate protein once the building stones are absorbed. Indeed, observations have been made by Hartmann and his associates⁸ on growing children which show that as much as 10 Gm. of protein per kilogram per day could be assimilated. Such a dose approaches the level achieved in experiment 3 in which a continuous intravenous injection was carried out for forty-eight hours. Whether such a high level of intake could be retained and utilized as well for longer periods remains for further study.

7. Elman, R.; Sachar, L. A.; Horwitz, A., and Wolff, H.: Regenerating Serum Albumin with Hydrolyzed Protein in Chronic Hypoproteinemia Produced by Diet, *Arch. Surg.* 44:1064 (June) 1942.

8. Hartmann, D. F.; Meeker, C. S.; Perley, A. M., and McGinnis, H. G.: *J. Pediat.* 20:308, 1942.

Of incidental interest are the figures for increase in total albumin observed in experiment 3. It will be noted that in dog 5, 3.4 Gm. of serum albumin was regenerated during the forty-eight hours during which 26.45 Gm. of nitrogen was retained. This amount of nitrogen would correspond ($\times 6.25$) to 165 Gm. of protein. The increase in serum albumin, therefore, represents 2.1 per cent of the nitrogen retained. In dog 6 the proportion is 2.4 per cent. In another paper³ it was pointed out that of the nitrogen retained in correcting a nutritional deficiency but a small percentage becomes available for synthesis of serum albumin. The figures obtained in these observations were somewhat higher than 2.1 and 2.4 per cent, but the general inferences are similar.

SUMMARY

Positive nitrogen balance as well as regeneration of serum albumin was demonstrated in protein-depleted dogs when 1.75 Gm. of nitrogen per kilogram per day was given for two days by means of a continuous venoclysis, an enzymic hydrolysate of casein containing a mixture of amino acids and polypeptides being used as the sole source of nitrogen. When this same total dose of nitrogen was given during twenty-four hours there was evidence of much less complete utilization.

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CARCINOID TUMORS (SO-CALLED) OF THE ILEUM

REPORT OF THIRTEEN CASES IN WHICH THERE WAS METASTASIS

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Carcinoid tumors are rare, but, judging from the volume of literature concerning them, probably few lesions of equal obscurity have received the same degree of attention. Moreover, the relatively common appendical carcinoid tumor has been superseded in point of interest by a small group localized elsewhere in the gastrointestinal tract, notably in the ileum. There are many reasons why this small group has merited what many believe to be unwarranted attention. Whereas appendical carcinoid tumors are often symptomless, those involving the ileum produce clinical evidence of obstruction in about one third of the cases, and small tumors thus located may produce major disturbances. Appendical carcinoid tumors are usually single, whereas about 25 per cent of their ileal counterparts appear as multiple tumor nodules.

But perhaps the most interesting feature connected with the group as a whole concerns the question of malignancy. Carcinoid tumors were regarded originally as ordinary (although small)¹ carcinomas, but the investigations of Oberndorfer² emphasized their essentially benign character, and the term "carcinoid" was coined to express the paradox of their malignant appearance contrasting with their benign clinical course. This view prevailed for a number of years, in spite of early (Ranson, 1890)³ evidence that metastasis occasionally takes place. Carcinoids then became "debatable tumors," with investigators contributing cases singly or in small groups. Many histogenic studies were attempted, and although no less than thirteen hypotheses of origin⁴ have been listed as "current possibilities," the majority of contributors felt with Masson⁵ that the tumors arise through a proliferation of chromoargentaffin cells native to the crypts of Lieberkühn. In the present paper no attempt will be made to detail the evolution of knowledge concerning carcinoids.

* Division of Surgical Pathology, Mayo Clinic.

1. Lubarsch, O.: Ueber den primären Krebs des Ileum nebst Bemerkungen über das gleichzeitige Vorkommen von Krebs und Tuberkulose, *Virchows Arch. f. path. Anat.* **111**:280-317, 1888.

2. Oberndorfer, S.: Karzinoide Tumoren des Dünndarms, *Frankfurt. Ztschr. f. Path.* **1**:426-432, 1907.

3. Ranson, W. B.: Primary Carcinoma of the Ileum, *Lancet* **2**:1020, 1890.

4. Collins, D. C.; Collins, F. K., and Andrews, V. L.: Ulcerating Carcinoid Tumor of Meckel's Diverticulum, *Am. J. Surg.* **40**:454-461 (May) 1938.

5. Masson, P.: Carcinoids (Argentaffin-Cell Tumors) and Nerve Hyperplasia of the Appendicular Mucosa, *Am. J. Path.* **4**:181-213 (May) 1928.

For this information the reader is referred to numerous excellent reviews.⁶ Our prime concern is an inquiry into the malignant propensities of these tumors—a fact still debated if not actually doubted by many.⁷

MATERIALS AND METHODS

Records from the Division of Surgical Pathology and the Section on Pathologic Anatomy of the Mayo Clinic were searched for cases in which the diagnosis was carcinoma, adenocarcinoma, carcinoid, argentaffin tumor, and so forth, involving the small intestine. Pathologic material from some 130 cases of such growths had been seen at the clinic between the years 1906 and 1943. This material was next obtained and studied in conjunction with clinical records in a weeding-out process designed to eliminate metastatic tumors from the series. Material from all "primary" growths was next studied, and sections were taken and examined by the rapid freezing technic, polychrome methylene blue being used as a stain. This procedure readily eliminated all but the obvious carcinoids and a small group of neoplasms which we labeled as doubtful until they were later accepted as examples of carcinoid tumors or rejected, on the basis of permanent hematoxylin and eosin preparations. The residual group of 30 specimens was then reassembled and reviewed in gross detail with special attention to the following features: the location of the tumor in relation to the ileocecal valve, and when possible to the mesenteric attachment; the size, shape, color, consistency and mode of origin (whether unicentric or multicentric) of the tumors; the mucosal relation, whether ulcerated or nonulcerated, together with any tendency toward intussusception; the condition of the muscularis and peritoneum with special reference to infiltration, "buckling," myohypertrophy, obstruction and so forth; the condition of the mesentery in relation to invasion, the presence or absence of involved lymph nodes and the mode of such involvement, whether by direct extension, by lymphatic permeation or by the embolic route. These and other pertinent data were recorded carefully for the purposes of analysis. Multiple blocks of tissue were then cut from the tumors. These were selected so as to include the junction of the mucosa with the tumor, the growing edge of the tumor, the peritoneal surfaces overlying and adjacent to the tumor and the adjacent mesentery with the involved and the uninvolved lymph nodes. In addition, sections were taken from the mucosa of the ileum proximal and distal to the growths, and from the appendix and the colon when available. All of these blocks were placed in a fresh 4 per cent solution of formaldehyde. They were sectioned at a thickness of 10 microns on a freezing microtome and stained routinely with hematoxylin and eosin. Residual portions of these blocks were prepared subsequently by the paraffin technic and were stained by the Galantha method for mucus. In addition, Becker's and Bielschowsky's methods were employed to demonstrate the specific argentaffin granules. In all, some 200 slides were made available for study.

6. (a) Ariel, I. M.: Argentaffin (Carcinoid) Tumors of the Small Intestine: Report of Eleven Cases and Review of the Literature, *Arch. Path.* **27**:25-52 (Jan.) 1939. (b) Cooke, H. H.: Carcinoid Tumors of Small Intestine, *Arch. Surg.* **22**:568-597 (April) 1931. (c) Forbus, W. D.: Argentaffine Tumors of the Appendix and Small Intestine, *Bull. Johns Hopkins Hosp.* **37**:130-153 (Aug.) 1925. (d) Gáspár, I.: Metastasizing "Carcinoid" Tumor of Jejunum, *Am. J. Path.* **6**:515-524 (Sept.) 1930. (e) Porter, J., and Whelan, C.: Argentaffine Tumors: Report of Eighty-Four Cases, Three with Metastasis, *Am. J. Cancer* **36**:343-358 (July) 1939. (f) Raiford, T. S.: Carcinoid Tumors of the Gastro-Intestinal Tract (So-Called Argentaffine Tumors), *ibid.* **18**:803-833 (Aug.) 1933. (g) Wyatt, T. E.: Argentaffine Tumors of the Gastro-Intestinal Tract: Report of Three Cases, One with Distant Metastases, *Ann. Surg.* **107**:260-269 (Feb.) 1938. (h) Masson.⁵

7. Cohn, S.; Landy, J. A., and Richter, M.: Tumors of the Small Intestine, *Arch. Surg.* **39**:647-660 (Oct.) 1939.

The central theme of this presentation concerns 13 of the 30 cases in which undoubted evidence of metastasis was found by the method outlined previously. Many of these lesions were not clinically silent. We believe, therefore, that the recording and the correlation, when possible, of clinical details with pathologic findings are necessary for a proper understanding of carcinoid tumors. In addition, it is hoped that the presentation of such a large series will open up new channels of investigation directed toward solving the problem of early diagnosis of carcinoid tumors, a problem which so far has not seen any satisfactory solution.

REPORT OF CASES

CASE 1 (Previously reported briefly ^{7a}).—A man aged 42 years came to the Mayo Clinic Aug. 7, 1940, because of five years of abdominal discomfort. His medical history was irrelevant. The illness of which he complained had taken the form of attacks of epigastric distress. Although pain was not an early complaint, the distress bore some of the clinical hallmarks of ulcer in that it was more or less periodic, came on about two hours after meals, lasted a variable time and then disappeared gradually. No nausea or vomiting had been noted, and "night pain" had not been experienced. During one of the episodes the distress amounted to a severe pain requiring morphine for relief. Operation had been advised but had been refused by the patient, who had been "carried over" on a medical regimen supplemented with "injections." Mild diarrhea had developed about two years after the onset of the trouble, and simultaneously the patient began to experience some distress in the lower portion of the abdomen. This distress, occasionally complicated by actual colicky pain, also came on soon after the ingestion of food and was accompanied by belching, flatulence, a feeling of fulness and an increase of the severity of the diarrhea. Occasional slight melena had been noted by the patient and had been attributed to hemorrhoids. Relief of symptoms by the use of special diets had been tried, but with no success, and the patient, who had been gradually lowering his intake of food in order to avoid abdominal discomfort, had lost weight progressively.

Essential positive findings on examination were limited to the observations of mild wasting, slight exophthalmos (unilateral and congenital), internal hemorrhoids and a firm, movable, nontender mass located in the left hypochondrium. The mass was estimated to measure 8 cm. in diameter and was believed to be a mesenteric cyst.

Results of hematologic examination and analysis of gastric contents were normal. Urinalysis revealed mild albuminuria with pyuria. Results of roentgenologic examination of the stomach and colon were interpreted as not revealing any intrinsic abnormalities. The presence of small bilateral renal calculi (clinically silent) was demonstrated on roentgenograms of the kidneys, but it was ascertained on the basis of further urologic investigation that renal function was good.

Exploratory laparotomy was performed through a low midline incision on Sept. 16, 1940. At operation multiple tumors of varying size, involving the ileum and its mesentery, the regional nodes and the parietal peritoneum were observed. In addition, small masses, obviously metastatic, were felt in the right and the left lobe of the liver. Several of the smaller nodules from the mesentery were removed for biopsy and were reported as carcinoid tumors on the basis of frozen sections, the polychrome technic of rapid staining being used. Accordingly 52 inches (132 cm.) of the terminal portion of the ileum was resected in a procedure designed to include all of the intrinsic tumor nodules and the regional nodes. The severed ends of the ileum were next closed and gastrointestinal continuity was reestablished by means of side to side ileoileostomy. On examination the appendix was ascertained to be normal and was not disturbed. Postoperatively a transfusion of whole blood was administered. The patient was dismissed fifteen days after operation, and when he returned for hemorrhoidectomy eighteen months later there was little evidence of deterioration of his condition. He was living and well when last heard from, twenty-eight months after his first admission.

Pathologic Data.—The surgical specimen consisted of 52 inches (132 cm.) of ileum, extending upward from a resection level some 10 inches (25 cm.) proximal to the ileocecal valve, and several small nodules of tissue removed from the pelvic peritoneum. Scattered throughout the resected segment were sixty-eight isolated orange-yellow nodules varying in diameter from 3.5 cm. to 2 mm. (fig. 1). These nodules were not by any means limited to, or even concen-

7a. Pennington, R. E., and Priestley, J. I.: Multiple Carcinoid Tumors of Small Intestine: Report of Case, Proc. Staff Meet., Mayo Clin. 18:49-51 (Feb. 24) 1943.

trated on, the antimesenteric border. (Such a localization has been discussed in the literature.⁸) All appeared to be covered at least in part by the mucosa of the intestine. In the case of the larger nodules some very superficial erosion of the mucosa was apparent and there was out-cropping of the underlying yellowish tumor tissue. These "raw surfaces" presented very little in the way of inflammatory reactions. In other words, the typical appearance of deep ulcers with necrotic bases was lacking, in sharp contrast to the picture seen in ordinary carcinoma of the ileum. With smaller lesions a deeper location seemed indicated. Some of the latter were present within the apexes of the transverse mucosal folds, whereas others lay more or less concealed in the intervening grooves. Several of the larger lesions, although relatively small, appeared to be producing obstruction by virtue of intussusception in addition to an observed tendency toward narrowing of the lumen through fibrous contraction. Proximal to these semi-obstructed zones the lumen of the ileum was dilated, the mucosa thrown into heavy corrugated folds pitted with superficial erosions and the muscularis considerably hypertrophied

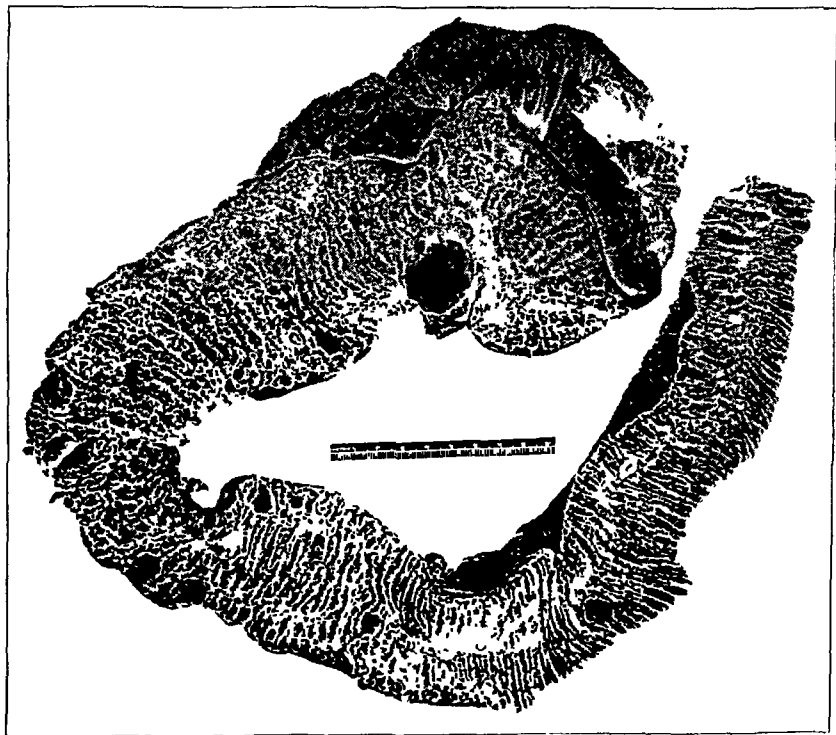


Fig. 1 (case 1).—Surgical specimen containing sixty-eight independent grade 1 adenocarcinomas (carcinoid type).

The peritoneum overlying several of the larger nodules was puckered and indurated in an obvious process of malignant infiltration. Smaller nodules did not demonstrate this form of extension, since they were grossly limited to the mucosa and submucosa. Mesenteric nodes were manifestly involved in several regions related to the larger lesions described previously. Primary and metastatic nodules, including those removed for biopsy from the pelvis, demonstrated the peculiar orange-yellow color so typical of carcinoid tumor.

Sixty centimeters from the lower end of the resected loop a Meckel diverticulum 2.5 by 2 by 2 cm. was found located, as is usual, on the antimesenteric surface of the ileum. It did not contain any tumor nodules. Likewise none was present in the proximal 25 cm. and the distal 8 cm. of the resected segment of ileum.

Microscopically, all of the tumors were typically carcinoid, and individually as well as in groups they duplicated practically all of the variations depicted in the literature on these tumors. Accordingly no useful purpose would be served by repeating a detailed description of all the histologic patterns encountered. On the other hand, the opportunity of studying so many

8. Pack, G. T., and Davis, A. H.: Carcinoid Tumors of the Small Intestine, *Am. J. Surg.* 9:472-477 (Sept.) 1930.

tumors, in various stages of evolution and occurring simultaneously in the same segment of ileum, brought out many features not to be observed in other cases. The following observations therefore deal primarily with these features.

1. Mucosa: In the case of the larger tumors superficial ulceration was present and in a few areas a thin layer of inflammatory granulation tissue covered the superficial aspects of the tumor. The ulcerations, however, could be termed little more than erosions and usually were located over the convexity of the underlying neoplasm (fig. 2*a*). More peripherally a submucosal infiltration was apparent with an elevation and stretching out of the crypts of Lieberkühn. The lack of deep ulceration was interpreted, after a study of the slides, as depend-



Fig. 2 (case 1).—Grade 1 adenocarcinoma (carcinoid) (hematoxylin and eosin): (*a*) superficial ulceration; the mucosa of the ileum is seen at the upper extremity; note the characteristic appearance of small, uniform, darkly staining tumor cells arranged in islands and cords ($\times 50$); (*b*) point of origin in base of a crypt of Lieberkühn; tumor cells palisaded peripherally; a group of granular (Paneth and Kultschitzky) cells are seen lining an adjacent crypt ($\times 200$); (*c*) origin of a tumor from a crypt in which mucous (X) and Paneth (Y) cells are still identifiable; note the uniformly small size of the tumor cells and the punctate basophilic granularity of their nuclei ($\times 620$).

ing on three prime factors which seemed to be in operation in all of the tumors examined: (1) an extreme degree of fibrosis between the islands of tumor tissue, (2) a strange lack of the necrosis so commonly observed in other forms of gastrointestinal malignant lesions and (3) a notable lack of vascularity. With some of the small tumor nodules the aforementioned erosion of the mucosa was minimal and occasionally absent.

Several of the nodules were small enough to demonstrate that a considerable portion of tumorous tissue lay superficial to the muscularis mucosae. In two of these, fortuitous sections actually demonstrated the histogenesis of the tumor cells through a process of budding from

the granular elements located deeply in a crypt of Lieberkühn (fig. 2 *b* and *c*). This finding substantiated the view that carcinoid tumors actually begin in the mucosa. Further support of this view was afforded by the observation that these small tumors, freed as they were from the effects of reactive fibrosis so prominent in larger lesions, presented beautiful evidence of formation of glands. Moreover, it was observed that (fig. 3 *a* and *b*) many of these glands assumed oval or elongated rather than rounded forms. (This finding was noteworthy, because it refutes the claim⁹ that the rounded "pseudo-acini" of carcinoids are rosettes and therefore probably of neuroectodermal rather than endodermal origin.) In many instances it was almost impossible to distinguish between the acinus-like groups of tumor cells and the "artefactitious" acini of the overlying crypts brought out by oblique sections; both contained granular cells and both gave evidence of secretion in that their lumens contained deposits. It was observed, however, that whereas mitotic figures were common in the cells lining the crypts, they were rarely observed in the groups of tumor acini. (When mitotic figures were observed

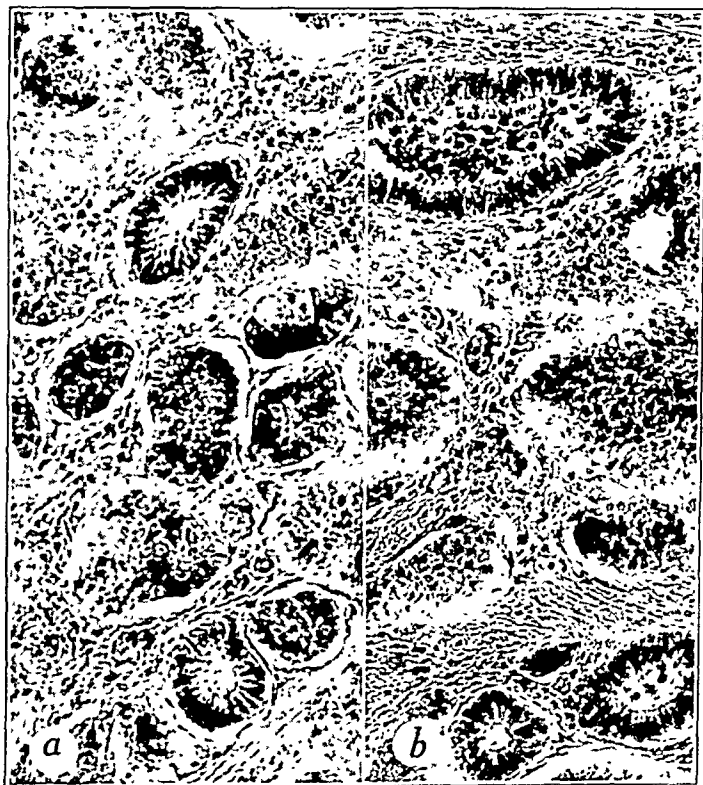


Fig. 3 (case 1).—Grade 1 adenocarcinoma (carcinoid). The illustration shows angular and oval tumor acini in addition to the rounded type (so-called rosettes of early writers). The stroma is only moderately fibrotic and certainly not vascular. (Hematoxylin and eosin; $\times 200$.)

there it was practically always in small mucosal tumors.) The aforementioned tumor acini, which were studied in careful detail and compared cytologically with the parent cells in the overlying mucosa, appeared to be differentiated to a large degree. This observation obtained also in a study of the larger (metastasizing) nodules.

It therefore became apparent (1) that the tumor cells arose from and produced true glandular spaces—hence that the neoplasms were true adenocarcinomas and (2) that considerable differentiation, histologically and cytologically, was present in the smaller tumors, and cytologically even in those in which the microscopic picture was modified by secondary changes, such as fibrosis. Accordingly the designation grade 1 adenocarcinoma (carcinoid) seemed applicable to each of the several nodules.

9. Lewis, D., and Geschickter, C. F.: Tumors of the Sympathetic Nervous System (Neuroblastoma, Paraganglioma and Ganglioneuroma), *Arch. Surg.* 28:16-58 (Jan.) 1934.

The muscularis mucosae always presented evidence of invasion, and in the majority of instances most of the tumorous tissue was situated outside rather than inside this layer. This observation is natural if one realizes that the point of origin of carcinoid is primarily the bases of the crypts which lie adjacent to the muscularis mucosae. Invasion of this layer appeared to result in thickening and fibrosis of a degree not observed in carcinoid cells invading the stroma of the mucosal glands. Along with the fibrosis there appeared to be a compression of the tumor cells, which no longer showed the numbers of typical acini described previously but rather had a tendency to grouping in strands and islands.

2. Submucosa and Muscularis: In the submucosa the groups of tumor cells again appeared in nests, islands or strands not presenting any unusual characteristics except a tendency to invade lymphatic spaces, especially those which were perineural. In the muscularis propria two features deserve mention: (1) considerable myohypertrophy associated with (or perhaps followed by) fibrosis and (2) invasion of the lymphatic spaces between the muscle bundles by tumor cells.

3. Peritoneum and Mesentery: Fibrosis was pronounced wherever the tumor cells were found and probably explained the "stenosis" of the intestine observed even with relatively small

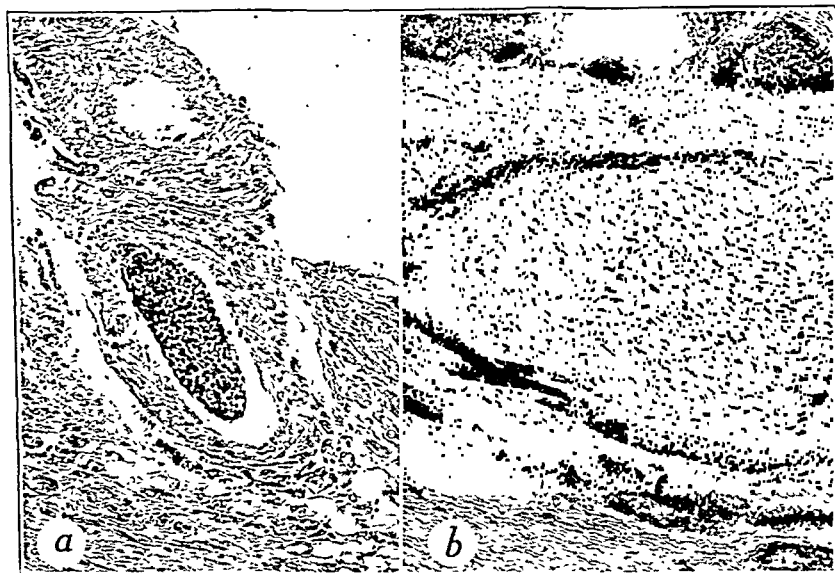


Fig. 4 (case 1).—Grade 1 adenocarcinoma (carcinoid) (hematoxylin and eosin $\times 100$): (a) tumor thrombus within the lumen of a vein; (b) invasion by tumor cells of the perineural lymphatic spaces. The nerve is hypertrophied but is by no means a neuroma.

carcinoid tumors. Extension of a tumor was characterized by four features: (1) direct extension, (2) invasion of blood vessels (fig. 4a), (3) invasion of ordinary lymphatic spaces and (4) a strong tendency to invade the perineural lymphatic spaces (fig. 4b). The nerves appeared to be hypertrophied, but whether as a result of work hypertrophy (obstruction of intestine) or of direct irritation could not be ascertained. There was no evidence of formation of neuroma.

4. Regional Nodes: Regional nodes were involved rather extensively by tumor, and in several instances the mode of spread was admittedly by direct extension. However, in other nodes located at some distance from the growth, embolic phenomena were present, with typical early carcinomatous invasion of the peripheral sinuses (fig. 5a). This we regarded as an important observation, refuting the view that the spread of carcinoid tumors does not represent true metastasis. Focal fibrosis of some degree was present in some regions, recalling the appearance of scirrhous carcinoma (fig. 5b). Other histologic features worthy of mention were the subacutely inflamed condition of the villous folds proximal to the major regions of tumor involvement and the presence of numerous acidophilic (Paneth¹⁰-Kultschitzky¹¹)

10. Paneth, J.: Ueber die secernirenden Zellen des Dünndarm-Epithels. Arch. f. mikr. Anat. 31:113-191, 1888.

11. Kultschitzky, N.: Zur Frage über den Bau des Darmkanals. Arch. f. mikr. Anat. 49:7-35, 1897.

cells in the mucosa of almost every specimen examined. Staining methods employing the principle of silver impregnation demonstrated that these cells contained granular elements similar to those of the cells of the tumor. However, lipid-containing vacuoles observed in the cytoplasm of the carcinoid cells did not have any counterpart in the mucosa as demonstrated by the sudan III method. Results of study by serial sections of grossly normal mucosa between adjacent tumor nodules indicated a multicentric mode of origin rather than spread from a single primary focus.

CASE 2.—A white man aged 78 first registered at the clinic on Feb. 19, 1941, complaining of "gas on the stomach" of four months' duration. Inquiry revealed that the patient's mother and one of his brothers had died of carcinoma of the stomach. The patient had been well previously except for an attack of appendicitis in 1930, which had been treated successfully by appendectomy.

The illness of which he complained had taken the form of abdominal distention and belching, gradual in onset, but complicated on three occasions by episodes suggesting intestinal obstruction. On each occasion hospitalization and treatment with "nasal suction" had been necessary. The last of these three attacks had begun three days prior to admission and had persisted with some recent abatement.

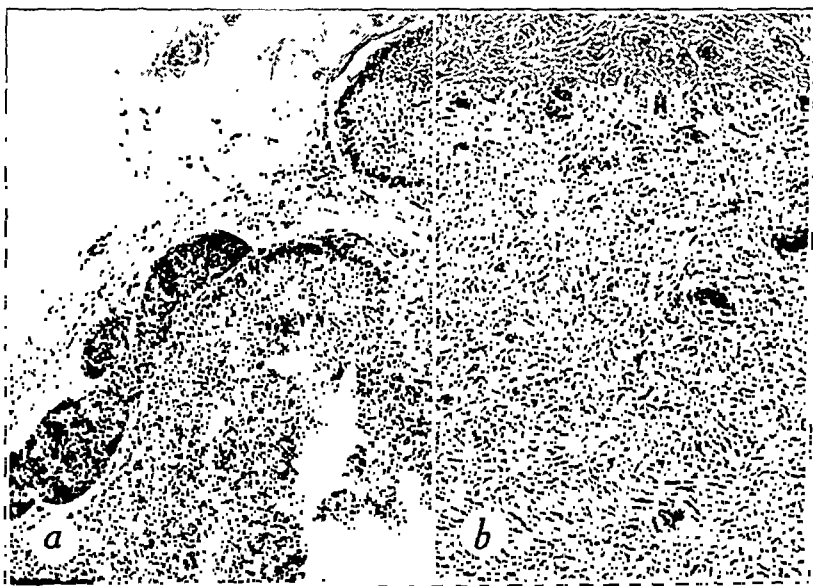


Fig. 5 (case 1).—Grade 1 adenocarcinoma (carcinoid) (hematoxylin and eosin): (a) "carcinoid" cells apparently still limited to the peripheral sinus of a lymphatic node ($\times 70$); (b) fibrosis about the tumor cells in this node recalls the picture of scirrhus carcinoma ($\times 100$).

Examination disclosed an undernourished, obviously dehydrated white man whose abdomen was moderately distended and tympanitic. Borborygmus was present and peristalsis was easily visible through a thin abdominal wall. No masses were palpable in the abdomen. Rectal examination disclosed what was interpreted clinically as benign prostatic hypertrophy, grade 3 (on the basis of 1 to 4). After a three day period of observation in which medical treatment succeeded in relieving in large degree the clinical signs of intestinal obstruction, proctoscopic and roentgenologic investigations of the rectum and colon were carried out. In the latter examination it was ascertained that the cecum was deformed by an extrinsic lesion which was interpreted as probably originating in the terminal portion of the ileum. Results of other laboratory examinations were essentially normal.

Inasmuch as the clinical history pointed rather strongly to the obstructive nature of the lesion, it was judged unwise to attempt further localization by means of roentgenologic examination of the small intestine after a barium meal. Accordingly abdominal exploration was proceeded with on Feb. 25, 1941, through a right rectus incision. An obstructive lesion was encountered in the terminal portion of the ileum, just proximal to the ileocecal valve. The lesion was so bound down as the result of local infiltration that resection was deemed out of the question. Nodules, obviously metastatic, were felt and seen underneath the capsule of the liver, and firm, yellowish nodules of a similar character involved the nodes of the

ileocecal angle as well as the omentum. One of these nodules (omental) was removed for biopsy, and the operation was completed with a side to side ileotransversostomy designed as a short-circuiting procedure. Postoperative convalescence was extremely smooth, and the patient returned to his home on the nineteenth postoperative day. One year later his wife informed us by correspondence that he had gained 10 pounds (4.5 Kg.) and was able to do some work on the farm. She wondered if the condition was "really cancer."

The nodule removed for biopsy was firm and orange-yellow on section. Microscopically the routine hematoxylin and eosin stains of sections as well as several standard "silvering" technics left no doubt as to the diagnosis of grade 1 adenocarcinoma (carcinoid) (fig. 6*a*).

CASE 3.—A single white woman aged 63 years first registered at the clinic on Dec. 11, 1940, because of "hot flushes and swelling of the face," of four years' duration. Her past medical history had been irrelevant. The only symptoms referable to her gastrointestinal tract were brought out by leading questions, in answer to which the patient admitted she was "occasionally bothered with cramps and that her appetite had been poor for several years." She had never suffered from constipation or diarrhea and had never noted blood in the stools. Her weight had been maintained fairly well.

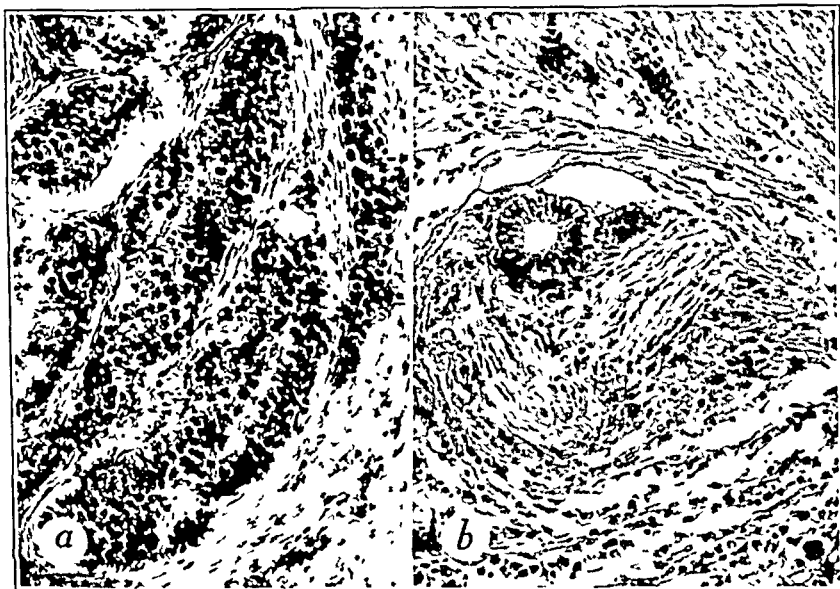


Fig 6—Grade 1 adenocarcinoma (carcinoid) (hematoxylin and eosin): In *a* (case 2) is seen an omental nodule showing dark-staining small cells grouped in cords and columns. Fibrosis is pronounced, and there are no acini present. The tumor is extremely cellular, and yet there are no mitoses ($\times 200$). In *b* (case 3) is shown a tumor acinus formed within a perineural lymphatic space ($\times 145$).

The essential finding on examination was a firm, nontender, somewhat movable mass, estimated to measure 6 cm. in diameter and located in the right lower quadrant of the abdomen. The mass did not move with respiration. Special dermatologic examination failed to reveal an actual cause for the attacks of facial erythema, but this condition was not believed to be related in any way to the intra-abdominal mass. Roentgenograms of the colon were interpreted as revealing a carcinoma in the region of the ileocecal valve.

Surgical exploration was performed on Dec. 16, 1940 through a primary right rectus incision. A neoplastic lesion was found involving the ileocecal region with nodular infiltration of the lymph nodes and other tissues in the ileocecal angle. Similar nodules were present throughout the liver. Resection of the portion of bowel containing the primary lesion was decided on after a fresh tissue diagnosis of carcinoid tumor. This resection included the removal of 15 cm of the terminal portion of the ileum, the cecum, the appendix and most of the ascending colon. Included also in the operative procedure was a fairly wide excision of the mesentery of the ileum with nodes in the region of major involvement. Continuity was reestablished by means of side to side ileocolostomy following inversion of the resected ends by several rows of sutures. The patient after passing through a somewhat stormy convalescence finally returned to her home on the thirty-ninth postoperative day.

In a recent communication her attending physician reported that the patient "had no complications and was really enjoying better health than one could expect."

The pathologic material consisted of 15 cm. of the terminal portion of the ileum, the cecum, the appendix and 20 cm. of ascending colon preserved in a 4 per cent solution of formaldehyde. Just at the ileocecal valve, partly in the cecum and partly in the ileum, was a firm, elevated, orange-yellow submucosal nodule measuring 3 by 3 by 2 cm., located on the mesenteric aspect as regards the ileum and showing a minimal amount of superficial ulceration. Mesenteric fat and mesenteric nodes in the ileocecal angle were obviously the seat of metastatic tumor deposits. On sectioning, the primary lesion was seen to involve both sides of the ileocecal valve in a "projecting" or semi-intussuscepting manner with evidence of obstruction manifested by some proximal dilatation of the ileum. No other lesions were found on careful examination of the remaining portions of the resected segments. The appendix was patent except at its tip and did not contain any carcinoids.

Salient microscopic features of this typical grade 1 adenocarcinoma (carcinoid) were as follows: (1) a minimal amount of superficial ulceration, the mucosa being thin and atrophic in appearance and covering all but the more central portions over the convexity of the tumor; (2) almost perfect reproduction of small acini by the tumor cells in the regions not affected by fibrosis (mucosal surface of tumor, several regional nodes, and certain of the perineural lymphatic spaces [fig. 6 b]); (3) absence of necrosis; (4) extensive fibrotic reaction around deeply located nests of tumor cells; (5) the occurrence of myohypertrophy in zones of tumorous invasion; (6) hypertrophy of nerve bundles in the mesenteric fat and invasion by tumor cells of the perineural lymphatic spaces; (7) invasion of blood vessels, and (8) true metastatic involvement of lymphatic nodes by the embolic route. In this, as in all other cases in which a segment of involved intestine was available for study, routine stains and other impregnation methods revealed the presence of Paneth and Kultschitzky cells in the "normal" mucosa.

CASE 4.¹²—A white garage mechanic aged 60 years registered at the clinic on July 2, 1926, complaining of "stomach trouble" of six months' duration. The illness took the form of repeated attacks of sharp pain in the upper portion of the abdomen. This pain occurred in attacks which came on from fifteen to twenty times daily and lasted but a few minutes. They were not related especially to the taking of food and were not accompanied by nausea, vomiting, diarrhea or constipation. However, the patient's appetite had been poor ever since the onset of the trouble, and a loss of 10 pounds (4.5 Kg.) had been sustained.

Appraisal of his physical condition resulted in a tentative diagnosis of abdominal carcinomatosis with enlargement of the liver and nodules in the anterior abdominal wall. The exact location of the primary lesion was not ascertained on roentgenoscopic examination of the stomach and colon. While the patient was being prepared for laparotomy, signs and symptoms suggesting a perforated abdominal viscus suddenly developed. That a perforation had in fact occurred was determined through a small incision which revealed gas and fluid in the peritoneal cavity. The condition of the patient was not such as to warrant even a minor attempt to localize the point of perforation, and accordingly drains were inserted. Death ensued twenty hours after operation.

Gross and microscopic features of the pathologic lesions in this case have been described previously by Cooke^{6b} (case 3) and will not be repeated. Pathologic proof of extensive hepatic metastasis was an outstanding feature.

CASE 5.—A practicing Spanish physician aged 63 years first registered at the clinic on Dec. 1, 1941, with the complaint of repeated attacks of abdominal cramps during a period of three months. His family history was irrelevant. His past medical history included several attacks of amebic dysentery from which complete recovery had ensued. A right inguinal hernia had been repaired in 1939, at which time apparently nothing was found to indicate a malignant process involving the cecum.

The illness of which the patient complained had begun on Sept. 7, 1941, when he ate rather generously of an astringent fruit which necessitated the taking of much water. About eight hours later he was seized with severe crampy supra-umbilical pain. This lasted several hours in spite of treatment with camphorated tincture of opium. It was accompanied by much borborygmus and followed by nausea and vomiting. However, a purgation with milk of magnesia apparently relieved the gastrointestinal disturbance, and no further trouble ensued for two months. On Nov. 10, 1941, the aforementioned symptoms returned, but in a more or less subacute or chronic form. Some abdominal distention was noted, as was also the fact that the taking of food aggravated the abdominal distress. On one occasion severe cramping pain developed, and for a time it was feared that emergency laparotomy would have to be resorted to. However, once again the acuteness of the episode subsided to such a degree that roent-

12. This case was reported previously by Cooke.^{6b}

genographic studies of the gastrointestinal tract were carried out. Results of these investigations indicated the presence of a lesion in the terminal portion of the ileum. Diverticuli were noted in the sigmoid portion of the colon. Examination of stools had failed to reveal any pathogenic amebas.

On examination at the clinic there was evidence of considerable loss of weight (7 Kg.). The abdomen was somewhat distended and tympanitic. No masses were palpable, but there appeared to be a localized zone of tenderness over the region of the cecum.

Roentgenograms of the stomach and cecum confirmed the information gained from a study of the previous roentgenograms. Inasmuch as the clinical history suggested a condition of intermittent intestinal obstruction, roentgenograms of the small intestine after a barium meal were not made.

At operation on Dec. 11, 1941, multiple, small, malignant-appearing nodules were found to involve the terminal portion of the ileum, the cecum and the first part of the ascending colon. Several nodes in the ileocecal angle were manifestly invaded. Accordingly resection was carried out, with removal of a portion of the terminal segment of the ileum, the cecum, the appendix and most of the ascending colon along with the local metastatic malignant deposits mentioned previously. Reestablishment of gastrointestinal continuity was effected by means of end to end



Fig. 7 (case 5).—Grade 1 adenocarcinoma (carcinoid) showing spread of tumor cells through mucosal lymphatics (hematoxylin and eosin; $\times 100$).

ileocolostomy. Seventy-five grains (5 Gm.) of powdered sulfathiazole was dusted over the peritoneum in the region of the anastomosis, and the abdomen was closed with continuous sutures of S. M. chromic catgut. A transfusion of citrated blood was administered at the conclusion of the operation. Postoperative convalescence was normal, and the patient left the hospital on the eighteenth day. When he was last seen, in February 1943, there was no clinical evidence of recurrence of tumor.

Pathologic material consisted of 20 cm. of the terminal portion of the ileum, the cecum, the appendix and 20 cm. of ascending colon along with a group of ileocecal nodes and a generous apron of mesenteric and pericolic fat. At the ileocecal valve, partly in the ileum and partly in the cecum, was a yellowish, firm, nodular tumor mass measuring 3 by 2 by 2 cm. This nodule showed only a small zone of superficial ulceration; the remainder appeared to be covered by a thin layer of mucosa; peripherally a certain degree of extension into the mesentery was apparent. Three centimeters proximally in the ileum was a similar but semipedunculated, intussuscepting, orange-yellow nodule 1.5 cm. in diameter and apparently independent of the first lesion. It too was firm in texture and appeared to be covered by a mucosal layer which was free from all but superficial ulceration. In the cecum at its junction with the ascending colon was a submucosal nodule 3 mm. in diameter, which might or might not be considered as entirely separate from the first lesion described. However, in the proximal portion of the

appendix were two submucosal nodules similar to the aforementioned but apparently separated from each other and from the larger lesions in the ileum and cecum; the terminal 6 cm. of the lumen of the appendix was obliterated and did not contain any tumors. Six nodes in the ileocecal angle were enlarged and firm. Metastatic involvement was evident from a typical orange-yellow color seen on sectioning. The only additional noteworthy feature consisted of a moderate dilatation of the ileum with thickening of the muscularis, proximal to the zone of malignant involvement.

Microscopically, for the most part, the various tumors duplicated the pictures described in connection with case 1. Invasion of veins was a noteworthy feature. A tendency to spread peripherally in the mucosal lymphatics was seen in several of the lesions (fig. 7). Pronounced hypertrophy of nerve bundles was apparent in connection with the largest nodule, and many of these nerve bundles were surrounded and invaded by cords of carcinoid cells.

CASE 6.—A white man aged 64 years visited the clinic on April 24, 1942, complaining of "stomach trouble." He had been well until 1933, when he began experiencing mild attacks of epigastric distress with distention. These attacks usually came on soon after eating, lasted several hours and then disappeared spontaneously. Dull pain, localized to the right of the umbilicus, occasionally accompanied these attacks. For several years the interval between consecutive episodes lasted one or two months, but thereafter it became shortened to a few weeks. Attacks became more severe and more definitely related to meals and were associated frequently with nausea. Relief by the use of alkalis was sought with moderate benefit only. In 1940, after the discovery of a mass in the abdomen, roentgenologic studies of the stomach and colon had been made. The seat of a healed duodenal ulcer was found, but it was not considered of much significance. Although no intrinsic lesion was found in the colon, fixation of the cecum was observed to be related to the abdominal mass, which was interpreted accordingly as being due to chronic inflammation—probably an old, resolved periappendical abscess. Surgical intervention therefore was not advised. The attacks of pain and discomfort continued and gradually assumed features indicative of subacute or chronic intestinal obstruction. There was considerable hiccorygmus; the passage of gas relieved the pain; the taking of food increased the discomfort and distention, and constipation was troublesome. However, in spite of all these symptoms the patient's general health suffered only mild deterioration, and there had been only a slight loss of weight.

Results of physical examination were essentially negative except for the finding of an enlarged prostate and the confirmation of a rounded, firm, nontender, semifixed abdominal mass estimated to measure 6 cm. in diameter and located just to the left of the umbilicus. Laboratory studies added little that was of diagnostic significance. Roentgenographic studies of the gastrointestinal tract were considered inadvisable in view of the patient's history. However, roentgenograms of the right renal region were useful in determining the extrarenal location of the aforementioned mass.

At operation on April 29, 1942 a malignant lesion was found in the terminal portion of the ileum. A huge, yellowish metastatic nodule involved the entire root of the mesentery. The liver contained similar yellowish nodules, obviously metastatic. Retroperitoneal lymph nodes also appeared to contain metastatic deposits, and one of these nodes was removed for biopsy. In spite of a fresh tissue diagnosis of grade 1 adenocarcinoma (carcinoid), it was judged that even a short-circuiting type of operation was out of the question, inasmuch as this would have meant sidetracking the entire small intestine to give relief from potential obstruction. Accordingly the incision was closed after exploration.

A recent communication from the patient read as follows: "It is now nine months since I left the clinic and my health is much improved over last year."

Pathologically the retroperitoneal node removed for biopsy proved typical of "carcinoid," with no noteworthy features except that it represented one of apparently many metastatic growths.

CASE 7.—A white traveling salesman aged 50 years registered at the clinic on April 7, 1924, complaining of crampy pains in the abdomen of six years' duration. Family and past medical records had been irrelevant except for an attack of typhoid fever from which the patient had suffered at the age of 16 years and from which recovery apparently had been complete.

The illness of which he complained had begun in 1918 with repeated attacks of mild to severe cramping pains in the midportion of the abdomen. These attacks had lasted for periods varying from hours to days and had been accompanied frequently by diarrhea and occasionally by the passage of dark-colored stools. The taking of food invariably had increased the severity of the pain and sometimes had resulted in regurgitation. Very little abdominal discomfort had been present between the attacks. Although the episodes had increased both in frequency and in duration over the period of the patient's illness, there had been surprisingly little deterioration of his general condition, and his weight had been maintained fairly well. Three weeks prior

to admission to the clinic appendectomy had been performed, and the surgeon had discovered a tumor involving the terminal portion of the ileum.

Results of physical examination were mainly negative except for the presence of mild abdominal distention. Laboratory studies added little of diagnostic import. In view of the surgical findings at the recent exploration it was deemed unnecessary to carry out roentgenographic examination of the gastrointestinal tract.

At exploration on April 15, 1924, a tumorous mass was located in the region of the ileocecal valve and short-circuited by means of a side to side ileocolostomy. On May 5, 1924, the growth was mobilized and removed along with 40 cm. of the terminal portion of the ileum, the cecum and most of the ascending colon. The procedure was planned so as to include in the resection a wedge-shaped portion of the mesentery which appeared to contain a number of indurated nodes at the ileocecal angle. No hepatic metastasis could be demonstrated by palpation. The severed ends of the ileum and colon were inverted as usual, and the abdomen was closed in layers. The patient made an uneventful convalescence and was alive nineteen years after operation.

The material for pathologic study consisted of 40 cm. of the terminal portion of the ileum, the cecum and 20 cm. of the ascending colon. Just above the ileocecal valve was an orange-



Fig. 8 (case 7).—Portion of a surgical specimen illustrating the "buckling" produced by small carcinoid tumors (possible roentgen sign).

yellow submucosal tumor measuring 4 by 3 by 2 cm., which projected into the ileum after the manner of an intussuscepting lesion, noticeably narrowing the lumen of the bowel at this point (fig. 8). Extension into the mesentery was apparent, as was also involvement of several lymph nodes at the ileocecal angle. In one of these, invasion by way of direct extension was apparent; in two nodes, situated at least 3 cm. from the nearest point of neoplastic extension, metastasis by way of lymphatic emboli seemed obvious. When the tumor was sectioned in a plane parallel to the longitudinal axis of the ileum, it was seen that involvement was mainly on the mesenteric aspect and that the muscularis propria was thrown up into the form of an inverted V, both sides of which were flanked by yellowish masses of tumor cells. This appearance further strengthened the conviction that the neoplasm had produced symptoms by causing intussusception. The ileum proximal to the point of obstruction was dilated and the muscularis presented evidence of work hypertrophy. An extreme degree of myohypertrophy was apparent in the zone of tumor infiltration. The cecum appeared normal on surface view. However, careful section of the mucosa brought to light a hitherto undiscovered yellowish nodule 3 mm in diameter, entirely separate from the main tumor mass but demonstrating in miniature all the characteristics of an early carcinoid tumor.

Microscopic study of the ileocecal lesion did not bring to light any features which have not been described already in connection with cases 1 to 5. The cecal lesion was partly mucosal and partly submucosal, apparently independent in origin from the large growth and therefore

"innocent" according to the standards of those who regard most carcinoids as benign. Nevertheless, in this small growth actual beginning invasion of a fair-sized vein was observed (fig. 9).

CASE 8.—An automobile mechanic 50 years of age was referred to the hospital after admission to the clinic on Sept. 19, 1941. The illness that led to his admission was typical of an attack of acute appendicitis, of thirty-six hours' duration. The attack climaxed a series of several following his first in 1923. Between attacks the patient had been in good health. A six year history of constipation with occasional bloating might or might not have been interpreted as being of importance in the light of subsequent observations. (This history was obtained by questioning the patient after his operation.)

Exploration performed through a primary McBurney incision on the right side revealed, in addition to an acutely inflamed condition of the appendix, a tumor involving the terminal portion of the ileum. Accordingly the primary incision was closed and a right rectus incision made. One stage removal of the terminal portion of the ileum, the cecum, the appendix and the ascending colon was performed, with inclusion of a generous segment of mesentery ascertained to contain a number of enlarged, indurated nodes. End to end ileocolostomy reestablished gastrointestinal continuity. Raw surfaces were peritonized carefully, and 5 Gm. of sulfanilamide powder was dusted about the line of anastomosis. Postoperatively a transfusion of



Fig. 9 (case 7).—Grade 1 adenocarcinoma (carcinoid). This small tumor had not metastasized and accordingly would be considered benign by some. However, note beginning invasion of a large venous channel. (Hematoxylin and eosin; $\times 100$.)

citrated blood was administered. After a somewhat stormy convalescence the patient left the hospital one month postoperatively. At the end of a twenty month period of subsequent observation he had not experienced any recurrence of trouble.

The operative material consisted of 20 cm. of the terminal portion of the ileum with an attached portion of the mesentery, the cecum, the appendix and 15 cm. of the ascending colon. Grossly the appendix was inflamed acutely but unperforated. In the ileum, 5 cm. above the ileocecal valve and on the mesenteric aspect, appeared a firm, orange submucosal nodule measuring 2 by 2 by 0.5 cm. No ulceration was apparent. The lumen of the ileum was somewhat narrowed at the level of the tumor and was mildly dilated proximally. Sections through the tumor revealed central extension into the mesentery. Peripheral invasion of the muscularis and the peritoneum was apparent, with puckering of the former and moderate hypertrophy of the latter. Eight regional nodes appeared to be involved by tumor, and in three of these the possibility of spread by direct extension was precluded by a location at some distance from the nearest point of infiltration. No tumorous involvement was found in the cecum or in the appendix.

Microscopically the lesion was a typical carcinoid. Unusual features were a relative lack of fibrosis about groups of tumor cells in the regional lymphatic nodes and the formation within these nodes of tumor acini (fig. 10 *a*). Some slight variation of size of nuclei also was observed, with occasional multinucleated forms. These were taken to represent a process of amitotic division (the apparent mode of "reproduction" in carcinoid tumors) and the lesion accordingly was still classified as a grade 1 adenocarcinoma (Broders).

CASE 9.—A white married woman aged 39 years registered at the clinic on Oct. 26, 1931, because of pain in the right lower quadrant of the abdomen of ten months' duration. She had been well until the late summer of 1930, when a swelling had appeared in the abdomen. Operation had been performed with the removal of "double ovarian cysts," which she was assured were benign. Ever since her operation the patient had been conscious of a dragging pain in the right lower abdominal quadrant. Severity of the pain varied considerably, but it was never sharp enough to require morphine for relief, and although several of the more recent episodes had been accompanied by borborygmi, no change had been noted in her intestinal "habits." Her appetite had remained good, and there had been no appreciable loss of weight.

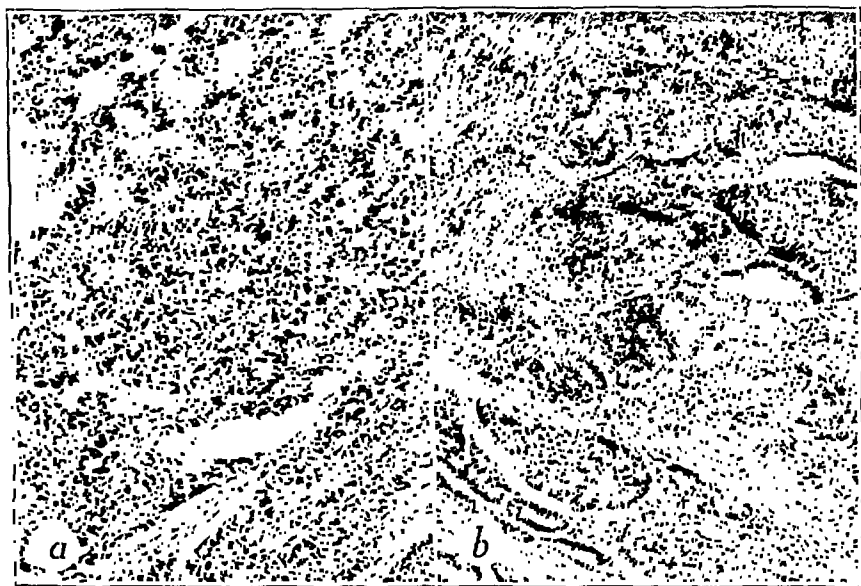


Fig. 10.—Grade 1 adenocarcinoma (carcinoid) (hematoxylin and eosin; $\times 100$): In the nodal metastasis seen in *a* (case 8) fibrosis is minimal and the cells are differentiating to form acini; we do not believe these spaces represent rosettes. In *b* (case 9) is seen the mucosal surface of a tumor showing numbers of rounded and angular acini; the latter form is important in identifying these hollow structures with true acini and is an important index of cellular differentiation.

The essential discovery on physical examination was a small, semifixed, slightly tender mass situated in the right lower abdominal quadrant and ascertained on bimanual pelvic examination to be somewhat adherent to the right side of the uterus. Results of laboratory examination of blood and urine were normal. Roentgenograms made of the colon were interpreted as not revealing any intrinsic abnormality, but the terminal portion of the ileum was poorly visualized on the roentgenograms. At operation on Oct. 28, 1931, the diagnosis of adenocarcinoma (carcinoid) was made by means of biopsy of a mesenteric node. The primary lesion, located in the terminal portion of the ileum, was accordingly short-circuited through a side to side ileotransversostomy. Appendectomy was performed. On Nov. 23, 1931, the growth was mobilized and removed along with the portions of the ileum, the cecum and the colon between the limbs of the former anastomosis. The open ends of the ileum and colon were inverted in the usual manner. Because of the poor condition of the bowel, performance of an additional ileocolostomy was necessary. The patient returned to her home one month later. When she returned to the clinic in May 1932 she stated that she had continued to have some abdominal distress with bouts of diarrhea. However, there was no

unequivocal evidence of a recurrence of her malignant process, and the diarrhea responded satisfactorily to dietary regulation plus the use of kaolin. Supplementary vitamins also were prescribed.

On June 17, 1936, a communication from her attending physician stated that a large fixed tumor involving the left upper portion of the abdomen had developed. It was his considered opinion that the mass was malignant. Death occurred on Nov. 23, 1936.

Pathologic material consisted of the mesenteric node and the appendix removed at operation on Oct. 28, 1931, and 40 cm. of the terminal portion of the ileum, the cecum, the ascending colon and a portion of the transverse colon from the operation on Nov. 23, 1931. Grossly and microscopically the appendix presented the changes of chronic appendicitis. No tumor nodules were found. The firm, orange mesenteric node was typical of carcinoid tumor. In the submucosa of the ileum, just proximal to the ileocecal valve, was a firm, yellowish orange nodule 2 cm. in diameter and presenting a small region of shallow mucosal ulceration. Previous sectioning of the specimen made it impossible to ascertain the exact relation of the growth to the mesenteric attachment and the degree of obstruction produced. Indirect evidence for obstruction was seen in the proximal portion of the ileal segment where dilatation of the lumen was present with thickening of the muscular coat. Infiltration of the mesentery was observed and several nodes appeared to be metastatically involved. Lesions were not observed in the cecum or the colon.

An interesting microscopic feature, in addition to the nodal metastasis and the invasion of several perineural lymphatic spaces and one small venous channel, was the finding in the mucosa of almost perfect tumor acini. These demonstrated oval as well as rounded lumens, and in some portions it was difficult to decide which acini were tumorous and which belonged to the glands of the normal mucosa (fig. 10 b).

CASE 10.—A white man aged 65 years visited the clinic on Dec. 4, 1939, complaining of pain in the abdomen of seven years' duration. His family and past medical histories contained no pertinent data. The illness of which he complained had begun seven years previous to registration with recurrent attacks of "knifelike pain" localized to the right midportion of the abdomen. These attacks of pain, which came at three to four month intervals, would last for ten to thirty minutes and usually were accompanied by nausea and occasional vomiting. Vomiting seemed to relieve the pain. Three years prior to the patient's admission to the hospital the character of the pain had changed to a dull ache which was more or less continuous. The location also shifted, the maximal discomfort changing to the right lower abdominal quadrant. Vomiting became infrequent. Six months prior to registration diarrhea had developed. This had continued in an episodic manner with an average of six to ten stools daily. Blood had never been noticed. A loss of some 20 pounds (9.1 Kg.) had been sustained over a twelve month period prior to admission.

Examination disclosed a somewhat ill-appearing white man suffering from mild abdominal distention. Peristalsis was visible through a thin abdominal wall. In the right lower quadrant of the abdomen a large mass was palpable, and the tissues in the abdominal parietes overlying the mass were locally indurated and somewhat nodular. The joints of the fingers, hands and ankles were somewhat swollen and stiffened in what was interpreted clinically as chronic infectious arthritis. Laboratory studies revealed the presence of gastric achlorhydria and mild secondary anemia. Albuminuria was graded 1 (on the basis of 1 to 4). Roentgenograms of the stomach and colon did not reveal any intrinsic abnormality.

At exploration on Dec. 9, 1939 a mass was found involving the terminal portion of the ileum and the regional nodes. Coils of intestine were matted together in the vicinity of the growth. No definite metastasis could be palpated in the liver, but numerous "implants" were present in the omentum and over the parietal peritoneum. One of these implants was removed for biopsy. Inasmuch as the patient stood the operation poorly, and in view of the fact that the clinical signs of intestinal obstruction were rather mild, it did not seem advisable to proceed with a short-circuiting type of operation. The incision was accordingly closed after exploration.

The material available for pathologic study consisted of a small nodule of tissue removed from the peritoneum of the anterior abdominal wall. The yellow color and firm texture were typical of carcinoid tumor. Microscopic sections on slides were prepared by routine methods and by the silver impregnation technic. No nerves appeared in the sections, and the veins did not appear to be involved. Pronounced fibrosis was evident about the clumps of tumor cells.

CASE 11.—A white woman aged 57 years registered at the clinic on Nov. 27, 1930, complaining of symptoms referable to carcinoma of the rectosigmoid. After preliminary colostomy on Dec. 1, 1930 the growth was removed by posterior resection. Radium needles were inserted in the posterior wound with a view to controlling the spread of local metastatic deposits which were ascertained to be present around the bases of the broad ligaments. The growth proved

to be an infiltrating grade 2 (Broders) adenocarcinoma of the type ordinarily seen in the colon and rectum. Nodes were involved metastatically. The carcinoma recurred locally, and the patient subsequently returned on several occasions for further therapy with roentgen rays and radium. However, her condition progressively deteriorated, and death ensued on Nov. 6, 1931.

At necropsy an independent carcinoid tumor measuring 1.5 cm. in diameter was found involving the terminal portion of the ileum just lateral to the mesenteric aspect. The growth was submucosal and yellow, but although productive of local scarring resulting from peritoneal extension, it had not compromised the lumen of the ileum materially. Two regional mesenteric nodes were firm and yellowish and obviously represented metastasis. It was the consensus that the lesion in the ileum, however interesting, had not contributed materially to the patient's death. The case illustrates again how a carcinoid may metastasize at an early stage of its evolution.

Microscopic features worthy of note were the lack of deep ulceration over the eroded surface of the growth, the "discontinuous" type of spread to the regional nodes (constituting therefore a true metastasis), the presence of granular cells in the mucosa of uninvolved portions of the ileum and the presence of occasional droplets of mucus within the lumens of tumor acini (fig. 11 *a*). The ileal tumor was quite dissimilar to the lesion in the rectosigmoid.

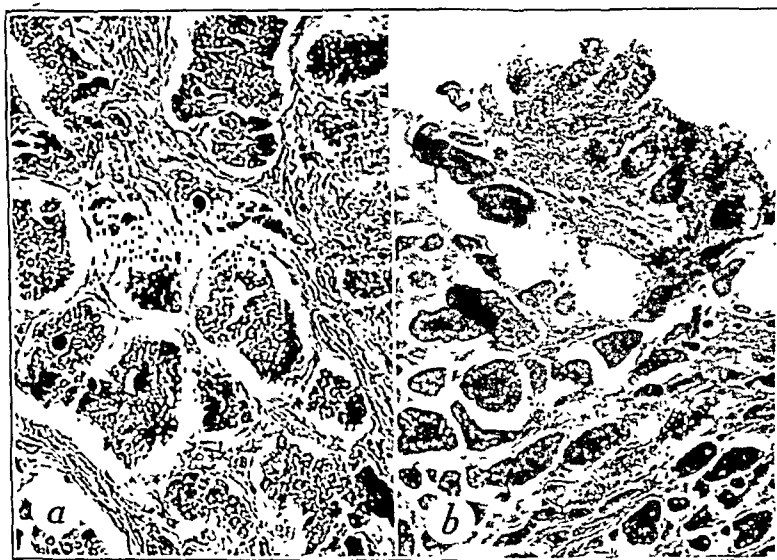


Fig. 11.—Grade 1 adenocarcinoma (carcinoid): In *a* (case 11) mucus, a rare finding in carcinoids, is depicted within three tumor acini (Galantha mucus stain; $\times 195$). In *b* (case 12) mucosal cells at the bases of crypts and cells of underlying tumors show blackening of argentaffin granules. (Bielschowsky method; $\times 100$.)

CASE 12.—An obese, multiparous woman aged 55 years visited the clinic on July 9, 1920, suffering from symptoms referable to a recurrent incarcerated umbilical hernia which had twice been reduced and repaired surgically. The hernia was again repaired but later again recurred. The patient succumbed at the age of 65 years after an episode of incarceration of her hernia. For five years prior to her death she had been suffering from moderately severe diabetes.

At necropsy several loops of gangrenous bowel were found in the recurrent hernial sac. Generalized peritonitis was present. Two orange-yellow submucosal nodules measuring 1.5 cm. and 8 mm. in diameter, respectively, were found in the ileum just above the ileocecal valve and nearer the mesenteric than the antimesenteric border of the ileum. Several nodes in the adjacent mesentery appeared grossly to be involved metastatically.

Microscopically both lesions proved to be typical grade 1 adenocarcinomas of the carcinoid type. Some superficial ulceration was present in the case of the larger lesion, but a thinned-out mucosa invested the surface of the smaller tumor. Impregnation of the tissues with silver (Bielschowsky method) produced a pronounced blackening of the cytoplasm of all the tumor cells and of the granular cells in adjacent zones of normal mucosa (fig. 11 *b*). Involvement

of the regional nodes appeared in this case to obtain, possibly on the basis of direct extension from the primary (larger) lesion. Lymphatics of the mesentery were permeated, but actual invasion of blood vessels was not observed. Of outstanding interest was the occasional production of small droplets of mucus demonstrated within the tumor acini by the Galantha method of staining for mucus. This phenomenon is to be interpreted in the light of incontestable evidence that carcinoids are of entodermal origin.

CASE 13.—A white woman aged 68 years came to the clinic on Sept. 8, 1931, complaining of "stomach trouble" of five months' duration. Her past medical history had been irrelevant. The illness of which she complained was described as an unusual "heaviness" in the midportion of the abdomen associated with belching and flatulence. Distress had been more or less constant but had been aggravated by the ingestion of food. She did not complain of any pain, nausea or vomiting, but an intermittent diarrhea, without blood, had been present since the onset of her other symptoms. In addition, there had been a loss of some 20 pounds (9.1 Kg.) over a four month period prior to registration.

On examination, emaciation of moderate degree was present. A semifixed mass, estimated to measure 8 cm. in diameter, was palpated in the right lower quadrant of the abdomen. Laboratory studies did not reveal anything of diagnostic significance, and roentgenograms of the stomach and colon were interpreted as being "negative for intrinsic disease."

At operation on Sept. 18, 1931, a tumor was found obstructing the terminal portion of the ileum. Primary resection of the terminal 40 cm. of the ileum, which contained the tumor, was performed. The distal end of the remaining portion of ileum was inverted and a lateral anastomosis made between it and the cecum in the region of the ileocecal valve. The appendix was normal in appearance and was not disturbed. Postoperative convalescence was normal, and the patient was dismissed from the hospital on the twentieth postoperative day.

Subsequent correspondence with the patient's attending physician revealed that "palpable liver metastasis developed within a period of months, and the patient died a routine carcinoma death in October 1933."

Pathologic material consisted of 40 cm. of the terminal portion of the ileum along with a small amount of mesenteric fat. No nodes were found on the specimen. Fifteen centimeters from the distal cut end of the ileum was an indurated, yellow, flat submucosal nodule measuring 1.5 cm. by 1 cm. by 5 mm. This nodule, which was located halfway between the mesenteric and the antimesenteric aspect of the bowel, appeared on section to infiltrate the wall as far as the serosa. Some local puckering and induration were present, and obstruction was evident in the form of thickening of the ileal musculature proximal to the growth. The mesentery of the ileum in the region of the growth did not appear grossly to be invaded by the tumor, whose nearest edge lay fully 2 cm. distant.

Microscopic sections made through the growth had the typical characteristics of grade 1 adenocarcinoma (carcinoid) as outlined for previous cases. Noteworthy local features were the almost intact condition of the superficial layer of the mucosa, the presence of one or two regions in which an origin of carcinoid cells could be traced to the bases of crypts and apparent myohyperplasia of the infiltrated muscularis propria. In keeping with the ultimate outcome of the case was the unexpected finding of strands of carcinoid cells infiltrating through the lymphatics of the mesentery, filling especially the perineural spaces in a veritable carcinomatous "neuritis." This mode of spread appeared to obtain on a true metastatic (embolic) basis, as no definite direct connection could be traced between the primary lesion and the mesenteric deposits.

ANALYSIS OF CLINICAL DATA

Incidence.—In the present series, carcinoid tumors comprised 23 per cent of all malignant neoplasms affecting the small intestine. The latter, according to Mayo and Nettrour,¹³ made up 0.47 per cent of all malignant neoplasms found in the entire gastrointestinal tract. Ariel,^{6a} in a comparable series, observed an incidence of 0.021 per cent for ileal carcinoid tumors. The incidence of appendical carcinoid tumors, as previously reported from this clinic by MacCarty and McGrath,¹⁴ was 0.47 per cent of all surgically removed appendixes. According to the literature localization in the appendix is two to ten times as frequent as in the

13. Mayo, C. W., and Nettrour, W. S.: Carcinoma of the Jejunum, Surg., Gynec. & Obst. 65:303-309 (Sept.) 1937.

14. MacCarty, W. C., and McGrath, B. F.: The Frequency of Carcinoma of the Appendix: A Report of Forty Cases, Ann. Surg. 59:675-689 (May) 1914.

ileum, while involvement of the stomach, duodenum, jejunum, Meckel's diverticulum, colon and rectum is uncommon.

Age.—The youngest patient in this series was 39 and the oldest 78 years of age; the average age was 58 years. This corresponds closely to the observation of Cooke,^{6b} who noted, on analyzing the literature, that the average age of patients who had metastasizing carcinoid tumors of the small intestine was 57.2 years. In the same analysis Cooke gave as 54.3 years the average age for 83 patients who had nonmetastasizing carcinoid tumors of the small intestine. The average age of patients who had appendical carcinoid tumors, on the other hand, was listed as 30 years by MacCarty and McGrath.¹⁴ The aforementioned observations accordingly lend support to the view early expressed by Burckhardt¹⁵ that metastasis from carcinoid tumors is merely a matter of time.

Sex.—In the present series 8 of the patients were men and 5 were women, a ratio which seems to have obtained throughout the literature on ileal carcinoid tumors. However, it appears that appendical carcinoid tumors are considerably more common among women than among men.

Symptoms.—Symptoms referable to "disturbed intestinal function" had been present in no less than 9 of the 13 cases in the present series (table 1) for an average duration of forty-two months. This incidence is high, if judged comparatively from reports in the literature. Cooke found the incidence to be 50 per cent for metastasizing carcinoid tumors but pointed out that pertinent clinical details were lacking in many of the remainder. A history suggestive of chronic, slowly progressive, intestinal obstruction was elicited from 8 patients. In contrast to a comparable group of cases of the "ordinary" type of ileal adenocarcinoma,¹⁶ these obstructive symptoms were usually mild, and the patients, on examination, appeared relatively well nourished. Obstructive features in these 8 cases often were described as episodic with crampy abdominal pain coming on in attacks, sometimes related to ingestion of food and occasionally relieved by regurgitation. Distention characteristically accompanied these attacks, which recurred with increasing frequency. Constipation was present in 3 cases, moderate to severe diarrhea in 2 and mild "looseness" in 1. In 6 cases one or more abdominal masses were clinically palpable. These masses were variously located, were semifixed, did not move with respiratory excursions of the diaphragm and were not tender or were only slightly tender. Melena, a symptom commonly observed in the "ordinary" type of ileal carcinomas and in malignant myomas, was observed in only 1 of our cases, and its origin was attributed to hemorrhoids. The infrequency of this symptom was in keeping with a notable absence of anemia.

In 3 of the cases there were no symptoms to indicate the presence of a lesion in the gastrointestinal tract. This group, however, represented a minority. It has become increasingly evident from the literature that one must abandon the original conception of carcinoid tumors as clinically silent neoplasms. Moreover, disturbances of major proportions have been recorded as resulting from carcinoid tumors which had not metastasized.

Laboratory findings, including the results of chemical examination of the blood, were not particularly helpful except as corroborative evidence supporting the clinical diagnosis of mild chronic intestinal obstruction. Hematologic studies rarely revealed any pronounced degree of anemia. Examination of stools for occult blood usually demonstrated traces of the latter, but in no instance were the

15. Burckhardt, J. L., cited by Cooke.^{6b}

16. Mayo, C. W.: Malignancy of the Small Intestine, *West. J. Surg.* **48**:403-407 (July) 1940.

stools, on examination, described as being tarry. These negative findings stood in observed contrast to those associated with "ordinary" types of carcinoma of the ileum, and in retrospect, therefore, they should perhaps be regarded as having been of some significance.

In the cases of more subacute obstruction in this series roentgenographic studies of the gastrointestinal tract were deemed inadvisable. In several instances in which the lesion involved the terminal portion of the ileum the presence of a deformity of the ileocecal valve suggested, but in no case actually decided, the nature of the lesion. Recently Miller and Herrmann¹⁷ described a roentgenologic sign which enabled them in 1 instance to arrive at the correct preoperative diagnosis of ileal carcinoid tumor. Acute "buckling" or kinking of the bowel is a common finding in cases in which carcinoid tumors have infiltrated the serosa. Although other lesions occasionally give rise to the same phenomenon, carcinoid tumor is the only *small* nonulcerated submucosal tumor in which this sign may be elicited. Reviewing in the literature the gross illustrations of "buckling" carcinoid tumors, one can see readily the possibilities for the use of Miller and Herrmann's sign in the preoperative diagnosis of a tumor which heretofore has always awaited identification by the pathologist.

Treatment.—In a relatively large number of our cases (85 per cent) the condition was a primary surgical problem, only 2 of the tumors being "accidental" necropsy findings. In 3 of the 11 cases in which operation was performed, the operation was confined to exploration with biopsy, because of widespread intra-abdominal metastasis and fixation of coils of intestine. In 1 case, in addition to the aforementioned procedure ileocolostomy was possible with short-circuiting of the growth. In 5 of the 7 remaining cases, one stage resection was effected even though 3 patients had hepatic metastasis at the time of operation. In 2 cases, operative removal in two stages was dictated by the general condition of the patient. Surgical treatment in every case was designed to be as radical as possible under the circumstances. Whereas one might have been chary of performing more than ileocolostomy for "ordinary" carcinoma of the ileum with hepatic metastasis, evidence has been afforded that in the case of carcinoid tumors growth of metastatic deposits may become "stationary"¹⁸ following removal of the primary tumor. Horsley¹⁹ advocated resection in cases of carcinoid tumor with metastasis, an opinion in which others concur. In these circumstances the pathologist familiar with methods of diagnosis by fresh frozen sections can offer valuable assistance to his surgical colleague.

Prognosis.—The life history of carcinoid tumors is one of slow evolution, with a long preoperative phase and with surprisingly long postoperative survival of patients so afflicted. Among the 11 cases in the present series in which operation was performed, 1 patient died several days after biopsy for an inoperable tumor. 2 patients succumbed two and five years after operation respectively, apparently as a result of local recurrence and metastasis, but the remaining 8 patients were living and "surprisingly well" for periods varying from ten months to nineteen years (table 1) even though several had hepatic metastasis. This parallels the experience of Terplan, Weintraub and Wolf,¹⁸ whose patient survived five years after ileocolostomy for carcinoid tumor with hepatic involvement. The death of

17. Miller, E. R., and Herrmann, W. W.: Argentaffin Tumors of the Small Bowel: Roentgen Sign of Malignant Change, *Radiology* **39**:214-220 (Aug.) 1942.

18. Terplan, K.; Weintraub, D., and Wolf, N. J.: Stationary Metastasizing Carcinoid of the Ileocecal Valve, *Arch. Path.* **30**:1155 (Nov.) 1940.

19. Horsley, J. S.: Carcinoma of the Jejunum and of the Ileum, *J. A. M. A.* **117**:2119-2123 (Dec. 20) 1941.

their patient occurred as a result of drowning, and at necropsy the "stationary" hepatic metastasis had not increased appreciably in size. Stewart and Taylor's²⁰ patient was alive ten years after development of metastasis, and Mallory²¹ recorded a similar case in which the patient survived for twenty years. Cameron²² stated that no less than 33 per cent of patients are alive at the end of eight years after operation for metastasizing carcinoid tumor. Thus, while death occurs as a result of carcinoid tumor (14 deaths from 1930 to 1939 according to Ariel's analysis of the literature), the outcome sometimes may be retarded by the simple procedure of ileocolostomy if surgical removal of the growth is impossible. Moreover, it has been suggested recently that postoperative roentgen therapy²³ may improve a prognosis which at worst is notably better than the outlook with the "ordinary" type of carcinoma of the small intestine.

TABLE 1.—*Metastasizing Carcinoid Tumors: Comparative Clinical Data*

Case	Sex	Age, Years	Symptoms and Findings	Duration	Operative Procedure	Outcome
1	M	42	Obstruction; diarrhea (mass present)	5 yr. 3 yr.	Primary resection	Well 28 months
2	M	78	Episodic obstruction	4 mo.	Exploration ileocolostomy	Well 1 year
3	F	63	"Cramps" and poor appetite (mass present)	2 yr.	Primary resection	Living 27 months
4	M	60	Crampy abdominal pain in attacks (masses present)	6 mo.	Exploration	Death (rupture of intestine)
5	M	63	Crampy abdominal pain in attacks	3 mo.	Primary resection	Living and well 14 months
6	M	64	Abdominal distress; pain; distention in attacks (mass present)	9 yr.	Exploration only	Living 9 months
7	M	50	Crampy abdominal pain in attacks	6 yr.	Preliminary ileocolostomy; secondary resection	Living 19 years
8	M	50	None (?) (mild constipation)	Primary resection	Well 20 months
9	F	39	Dragging pain (mass present)	10 mo.	Ileocolostomy; secondary resection	Died 60 months
10	M	65	Crampy abdominal pain in attacks (mass present)	7 yr.	Abdominal exploration	Unable to trace
11	F	57	None	Nonoperative	Necropsy observation
12	F	65	None	Nonoperative	Necropsy observation
13	F	68	Intestinal obstruction in attacks; diarrhea (mass present)	5 mo.	Primary resection	Death from carcinoma 2 years

PATHOLOGIC DATA

Location of Lesion or Lesions (table 2).—In all 13 cases the ileum was the primary seat of formation of tumor. In several instances in which multicentric nodules were present, additional points of localization were as follows: jejunum, 1 case; cecum, 1 case; cecum and appendix, 1 case. Among 9 cases in which the primary

20. Stewart, M. J., and Taylor, A. L.: Carcinoid Tumor of Appendix with Large Pelvic Deposits, *J. Path. & Bact.* **29**:136-139, 1926.

21. Multiple Carcinoids of Ileum with Regional Metastases, Cabot Case 26162, *New England J. Med.* **222**:684-687 (April 18) 1940.

22. Cameron, A. L.: Primary Malignancy of Jejunum and Ileum, *Ann. Surg.* **108**:203-220 (Aug.) 1938.

23. Bailey, O. T.: Argentaffinomas of the Gastrointestinal Tract, Benign and Malignant, *Arch. Path.* **18**:843-864 (Dec.) 1934. Klemperer, P., in discussion on Goldberg, S. A.: Unusual Neoplasms of the Small Intestine, *Am. J. Path.* **14**:663-664 (Sept.) 1938.

lesion could be localized definitely to a particular segment of intestine, this point of origin was the terminal portion of the ileum in 3 cases and the ileocecal valve in an additional 3. These findings are in keeping with the observations of Cooke^{6b} and of Raiford^{6c} that the majority of ileal carcinoid tumors seem to have a predilection for the terminal segment of the small intestine. None of these metastasizing carcinoid tumors originated in connection with Meckel's diverticulum. Hertzog and Carlson,²⁴ however, have reported from this clinic 2 nonmetastasizing carcinoid tumors thus originating.

Multicentricity.—Multiple carcinoid tumors occurring simultaneously in the same segment or in adjacent segments of intestine are regarded as multiple primary growths rather than as the result of metastatic spread from a single focus. In the

TABLE 2.—*Metastasizing Carcinoid Tumors: Comparative Pathologic Data*

Case	Location	Multi- centric	Relation to Mesentery	Size	Nodes and Fat (Involve- ment)	Nerves and Blood Vessels	Peritoneum and Liver *	
1	Ileum	+	(68)	Variable	2 mm. to 3 cm. diam.	Nodes + Fat +	Nerves + Vessels +	Peritoneum + Liver +*
2	Ileum	?	?	Large †	Nodes +* Fat +	Nerves ? Vessels ?	Peritoneum + Liver +*	
3	Ileocecal valve	0	Mesenteric	3 by 3 by 2 cm.	Nodes + Fat +	Nerves + Vessels +	Peritoneum + Liver +*	
4	Ileum and jeju- num	+	(15)	Variable	0.5 to 1.5 cm. diam.	Nodes + Fat +	Nerves + Vessels +	Peritoneum + Liver +
5	Ileum; cecum; appendix	+	(5)	Antimesenteric	2 mm. to 3 cm. diam.	Nodes + Fat +	Nerves + Vessels +	Peritoneum + Liver —
6	Ileum	?	?	Large †	Nodes + Fat +*	Nerves — Vessels —	Peritoneum + Liver +*	
7	Ileocecal region; cecum	+	(2)	Mesenteric	4 by 3 by 2 cm. and 3 mm. diam.	Nodes + Fat +	Nerves ? Vessels +	Peritoneum + Liver —
8	Ileum (terminal)	0	Mesenteric	2 by 2 by 0.5 cm.	Nodes + Fat +	Nerves + Vessels —	Peritoneum + Liver —	
9	Ileum (terminal)	0	?	2 cm. diam.	Nodes + Fat +	Nerves + Vessels +	Peritoneum + Liver —	
10	Ileum	?	?	Large †	Nodes ? Fat +	Nerves ? Vessels ?	Peritoneum + Liver —	
11	Ileum	0	Paramesen- teric	1.5 cm. diam.	Nodes + Fat —	Nerves — Vessels —	Peritoneum + Liver —	
12	Ileum (terminal)	+	(2)	Paramesen- teric	1.5 cm. and 8 mm. diam.	Nodes + Fat +	Nerves — Vessels —	Peritoneum + Liver —
13	Ileum	0	Paramesen- teric	1.5 by 1 by 0.5 cm.	Nodes — Fat +	Nerves + Vessels —	Peritoneum + Liver —	

* Ascertained at surgical exploration. No biopsy.

† Surgical description.

present series such a multicentric mode of origin was demonstrated in 5 of the 10 cases in which accurate information was available on this point. In 1 instance it was necessary to search rather carefully for the second tumor nodule, which lay semiconcealed beneath the mucosa of the cecum. Thus we confirmed the impression of other investigators who have estimated that 20 to 50 per cent of ileal carcinoid tumors occur as multiple tumors. The number of independent nodules in this series of cases varied from two to sixty-eight. In a search of the literature we have not found a record of any instance in which the number of nodules exceeded that demonstrated by our case 1. Multicentricity of ileal carcinoid tumors is a phenomenon which, although poorly understood as regards causation, nevertheless carries very clear implications from the standpoint of surgical treatment. More specifically, great care should be exercised at the time of operation to make

24. Hertzog, A. J., and Carlson, L. A.: Carcinoid of Meckel's Diverticulum, *Arch. Path.* 20:587-589 (Oct.) 1935.

sure that the limits of resection are extended widely enough so as to include all of the neoplastic nodules.

Relation of Tumor to Mesentery.—It has been stated⁸ that carcinoid tumors of the small intestine invariably arise along the antimesenteric border. In the present series, 9 of the specimens were in a state of preservation such as to allow one to determine the localization of the tumor in relation to the circumference of the ileum. In 2 instances the point of origin was exclusively antimesenteric, in 3 it was definitely mesenteric, in 2 it was paramesenteric and in the remainder a variable relation existed. It is therefore our opinion that carcinoid tumors may arise from any point along the circumference of the small intestine.

Size of Tumor.—Carcinoid tumors have been aptly termed "little carcinomas," but occasionally large specimens are encountered. The tumor in one of Bretschger's²⁵ cases was as large as a child's head. In the present series the largest of the primary tumors available for measurement was 4 by 3 by 2 cm. and the smallest 2 mm. in diameter. Our own material confirmed the view expressed by others that the metastatic deposits from carcinoid tumors frequently exceed in volume the primary nodules. Size was related to metastasis in a general way only, and some of the ileal carcinoid tumors not included in this series were larger than some in which metastasis had occurred.

Color of Tumor.—Carcinoid tumors are described almost universally as being yellowish.²⁶ All of the tumors in the present series were more orange than yellow. Mallory²⁷ too described carcinoid tumors as orange-yellow nodules and compared their color to that of the adrenal cortex. MacCarty and McGrath¹⁴ made a similar colorimetric distinction in connection with appendical carcinoid tumors. Whether or not carcinoid tumors are fundamentally yellow or orange, we believe that their color is so characteristic that it may often serve as an important factor in gross diagnosis at operation. A notable lack of necrosis is also useful in distinguishing these from other malignant tumors of the small intestine.

Mucosal Relation.—It is generally stated that carcinoid tumors are submucosal and are unassociated with superficial ulceration. Some authors state definitely that ulceration is never observed; others, including the majority, admit that ulceration is present but in the microscopic rather than the gross sense of the word. In the present series gross superficial ulceration was present in all of the larger nodules examined. In some of the smaller nodules ulceration was not obvious on gross inspection, but in nearly every instance microscopic sections demonstrated that the tumor cells had broken through to the surface at one or more points. It must, however, be emphasized that the ulceration present was shallow, with minimal amounts of necrosis and never with the overhanging edges so commonly seen in other types of gastrointestinal carcinoma. This fact has a most important bearing on symptomatology, as it explains why melena is rarely observed in connection with carcinoid tumors.

Relation to the Peritoncum and Muscularis.—Carcinoid tumors have great propensities to invade, being similar in this respect to "cylindromas" (which they indeed resemble otherwise).²⁸ It is thus not surprising that muscularis mucosae.

25. Bretschger, E.: Klinik und Prognose der Appendix- und Dünndarmcarcinoide, Deutsche Ztschr. f. Chir. **249**:297-316, 1937.

26. Huebschmann, cited by Cooke.^{6b} Bailey.²²

27. Carcinoid of Ileum, Cabot Case 26192, New England J. Med **222**:806-808 (May 9) 1940. Footnote 21.

28. Dockerty, M. B., and Mayo, C. W.: Primary Tumors of the Submaxillary Gland with Special Reference to Mixed Tumors, Surg., Gynec. & Obst **74**:1033-1045 (June) 1942

the submucosa, the muscularis propria and the peritoneum are invaded frequently by carcinoid cells. (Some investigators, including Cooke,^{6b} have accepted peritoneal invasion as a criterion of metastasis. We have not so regarded this direct mode of spread.) In the present series the muscularis mucosae was pervaded by tumor cells even in the smallest tumors, the majority of whose cells lay beneath this layer. Reactive hyperplasia was present, the muscular fibers furnishing a rather dense stroma for the carcinoid cells. In the larger examples the submucosa, the muscularis propria and the peritoneum always demonstrated tumorous infiltration, sometimes in impressive degree. Pronounced myohypertrophy and fibrosis were present. This observation has been repeatedly confirmed but variously interpreted. The condition has been regarded by some as a "work hypertrophy" incident to the development of obstruction. However, evidence that local irritative phenomena were probably the operative factors was furnished by the case of Stewart, Willis and de Saram,²⁹ in which a small carcinoid tumor arose from the intestinal portion of an ovarian teratoma. Here the factor of obstruction was eliminated; yet these authors observed the usual myohypertrophy in zones of muscular invasion. Peritoneal spread in several of the tumors resulted in puckering and acute "kinking" of the intestine at that particular site. The importance of this feature in producing obstruction is attested by numerous cases in the literature; the frequent production of the phenomena by these "little carcinomas" has opened an avenue which may possibly lead to correct preoperative diagnosis of carcinoid tumors by means of roentgen rays.

Involvement of Nodes and Mesenteric Fat.—Involvement of regional lymphatic nodes constitutes the commonest criterion for attaching the designation "metastasizing" to a carcinoid tumor. Such involvement was present in 11 of the 13 cases in our series. Moreover, in contradistinction to assertions in the literature indicating that spread of carcinoid tumors is by direct extension²³ (and therefore not a true metastasis), in many of our cases there was true embolic metastasis by way of lymphatic channels. In short, it appeared from a study of these nodes that the spread thereto did not differ in any essential regard from that developed with "ordinary" carcinoma of the small intestine even to the actual incidence of such involvement.³⁰ In 37 per cent of our 30 cases and in 84.6 per cent of those in which metastases had occurred there was nodal metastasis. Invasion of mesenteric fat, like invasion of the nearby peritoneum, was observed in all 13 cases, but such involvement was not always apparent on gross inspection. Oftentimes the strands of tumor cells extended for only a short distance into this adipose connective tissue, and in several instances they did not reach as far as the regional lymphatic nodes. In 1 case multiple blocks of tissue were necessary for microscopic demonstration of mesenteric infiltration. No nodes had been found on this specimen, and yet the patient had succumbed as a result of metastasis two years after operation.

Involvement of Nerves.—The relation of nerves to the spread of carcinoid tumors has long been an interesting problem.³¹ Masson⁵ even went so far as to

29. Stewart, M. J.; Willis, R. A., and de Saram, G. S. W.: Argentaffin Carcinoma (Carcinoid Tumour) Arising in Ovarian Teratomas: A Report of Two Cases, *J. Path. & Bact.* 49:207-212 (July) 1939.

30. Craig, W. McK.: Lymph Glands in Carcinoma of the Small Intestine: A Review of the Condition of the Glands in Carcinoma of the Gastro-Intestinal Tract, *Surg., Gynec. & Obst.* 38:479-485 (April) 1924.

31. (a) Humphries, E. M.: Carcinoid Tumors of the Small Intestine: A Report of Three Cases with Metastasis, *Am. J. Cancer* 22:765-775 (Dec.) 1934. (b) Kross, I.: Carcinoid Tumors of the Small Intestine, *Am. J. Digest. Dis.* 6:725-727 (Dec.) 1939. (c) Gáspár.^{6d} (d) Bailey.²³

state that the formation of a neuroma constitutes one stage in the development of an appendical carcinoid tumor. Investigators who have studied ileal carcinoid tumors, large and small, have been in universal agreement that no comparable neuromas are formed in this location. Many have observed hypertrophied nerves surrounded by carcinoid cells, however. In the present series actual invasion of nerves appeared to occupy a place secondary in importance to the phenomena of malignant infiltration of perineural lymphatic spaces. Such perineural involvement was found not only within the intestinal wall but to a lesser degree within the folds of the mesentery. The appearance at once recalled a similar observation made in connection with submaxillary adenocarcinomas of the cylindroma type.

Involvement of Blood Vessels.—Hepatic metastasis, in most cases of carcinoid tumor, supposedly stands as *prima facie* evidence of spread via the blood vessels. Although such a mode of dissemination has been considered as probable for a long time, actual demonstration has only occasionally³² afforded proof of the process. In the present series actual invasion of veins by thrombi of tumor cells was observed in 5 of 13 cases. In 2 additional cases the presence of hepatic metastasis indicated such a mode of spread, but biopsy material was inadequate for purposes of microscopic confirmation. Moreover, we have observed the phenomenon of blood vascular invasion in some carcinoid tumors which apparently had not yet metastasized and which, according to some investigators, would therefore be classed as benign.

Involvement of Liver.—Metastatic carcinoid involvement of the hepatic parenchyma is considered by some investigators to be almost half as common as metastatic spread to regional nodes. Cooke^{6b} found this ratio to be 4:5, and Ariel,^{6a} reviewing the literature from 1930 to 1939, submitted a ratio of 1:3. In the present series, if one accepts as authentic the surgical findings at exploration, hepatic involvement was observed in 5 cases, as against 11 cases in which carcinoid deposits occurred in regional nodes.

Malignancy of Carcinoid Tumors.—Some investigators feel that appendical carcinoid tumors are benign and that all extra-appendical examples are malignant; others concede that all metastasizing carcinoid tumors are malignant, whereas those which fail to spread are benign³³; others again express the view that all carcinoid tumors, regardless of size and location and localization or extension, are malignant histologically and should be treated as "cancers."³⁴ In the case of small intestinal carcinoid tumors, moreover, the implications of malignancy are now being widely considered in the clinical as well as the pathologic sense. From the evidence afforded, by the study of this series and a comparison with examples of nonmetastasizing members of this group, appendical,³⁵ ileal and colonic, we contend that all carcinoid tumors are malignant neoplasms arising from glandular epithelium and therefore carcinomas in every sense of the word. It has been our constant observation that so-called benign and malignant examples are identical histologically, with cellular uniformity the keynote of microscopic diagnosis. Mitoses are practically never encountered. The tumor cells are derived from glandular (entodermal) elements and in the mucosal aspects of the tumors frequently reproduce glandular

32. Gáspár.^{6d} Humphries.^{31a}

33. Ewell, G. H., and Jackson, R. H.: Carcinoid Tumors of the Small Intestine, with Case Report (Multiple Benign Embryonal Carcinoid Tumors), Wisconsin M. J. **30**:737-740 (Sept.) 1931. Lewis.⁹

34. Willis, R. A.: Argentaffin Carcinomata ("Carcinoids") of the Small Intestine, M. J. Australia **2**:400-403 (Oct. 26) 1940. Ranson.³ Gáspár.^{6d}

35. Hopping, R. A.; Dockerty, M. B., and Masson, J. C.: Carcinoid Tumor of the Appendix, Arch. Surg. **45**:613-622 (Oct.) 1942.

spaces which occasionally contain droplets of mucus. Formation of acini sometimes is also observed in metastatic (nodal) deposits. The tumor cells, arising as they do through differentiation from granular cells of the intestinal crypts, produce these same granules, which may be specifically identified by means of appropriate stains.

Because of the aforementioned facts we submit that the designation grade 1 adenocarcinoma (carcinoid) should be appended to all tumors of this type. Such a designation would remind one at once of their malignant capacities combined with an expected slow evolution. It would also denote an origin from a specific cell type as distinguished from the "ordinary" type of adenocarcinoma, which is frequently of much higher grade (Broders) and consequently of more rapid growth and dissemination.³⁶

SUMMARY

In a review of the records and pathologic specimens of 130 carcinomas of the small intestine, 30 so-called carcinoid tumors were encountered. Thirteen of these had metastasized locally or distantly. These 13 tumors affected persons in the older age groups and in 9 instances were responsible for disabling symptoms, chief among which were those indicative of chronic intestinal obstruction. Preoperative diagnosis of the type of lesion was not possible, but radical surgical procedures were carried out in the majority of cases, in accord with known results which had followed similar procedures used in dealing with carcinoid tumors. Fresh tissue identification of type was of considerable assistance in deciding this issue of treatment. Follow-up studies appeared to justify the type of treatment employed. Pathologically the neoplasms tended to be present in the terminal segments of the ileum as small orange submucosal nodules with minimal ulceration. In 50 per cent of the cases in which accurate information was available, the tumors were multicentric. There was pronounced infiltration of the submucosa, the muscularis, the peritoneum, the nerves, the lymphatic spaces and the blood vessels. Puckering and kinking in the region of tumor invasion were observed and may provide a valuable roentgenologic sign of identification. Involvement of regional nodes was observed in 11 and hepatic metastasis in 5 instances. Evidence was afforded on the basis of microscopic studies that all carcinoid tumors are in essence peculiar low grade (1, Broders) adenocarcinomas. It is suggested, however, that the word "carcinoid" be appended by virtue of customary usage and at the same time perhaps as a designation of the peculiar mode of origin, life history and spread of these rather unusual neoplasms.

The Mayo Clinic.

36. In 2 of our cases the simultaneous occurrence of the two types of adenocarcinoma was observed. This association has been noted recently by others (Warren, S., and Gates, O.: Multiple Malignancy with Metastasizing Carcinoid of Ileum and Miliary Tuberculosis, *Arch. Path.* 18:524-526 [Oct.] 1934. Humphries^{31a}), who also observed that the simultaneous occurrence of tuberculosis and carcinoid tumors (Primrose, A.: Primary Carcinoma of the Small Intestine in an Octogenarian, *Ann. Surg.* 82:429-435 [Sept.] 1925) appears to be on the decline.

AN OPERATION FOR SCAPHOCEPHALY

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BALTIMORE

Acrocephaly and scaphocephaly are related deformities of the skull in infants and children. They are due to unexplained premature closure of the cranial sutures and result in crowding the brain within a space that is too small for its present size and its subsequent growth. As a result the eyeballs may (or may not) protrude and the child is listless and mentally backward and has headaches. Papilledema is frequently present, and there is convolutional atrophy of the skull and compression of the ventricular system. All the signs and symptoms are the result of general intracranial pressure.

Operative relief of these conditions has only recently been reported by King (1941),¹ although a preliminary report was made in 1937, when the operation was first performed. Two cases were reported, and in 1 at least a brilliant result was evident four and a half years later. The patient's condition had seemed hopeless and his physical appearance was frightful but a fine-looking boy appears in the later photographs. Woodhall² performed the same operation on 2 patients with fairly similar deformities and produced definite improvement over a period of two years. King's procedure consists in cutting into loosely lying fragments most of the vault of the skull on both sides, thus allowing the cranial chamber to expand before the fragments reunite. Woodhall aptly terms it the "morcellation" method of King. King does not open the dura; it would probably be dangerous to do so with the bony fragments lying loosely on it. Although the dura is a tough, inelastic membrane, it doubtless yields in time to the intracranial pressure, just as it expands with the normal growth of the brain.

The purpose of this communication is to present a different operative attack for the same conditions. Instead of breaking up the bone into fragments, I have enlarged the cranial chamber by lifting most of each side of the skull. Two operations with an interval of two to three weeks or months are performed.

OPERATION

A large longitudinal incision beginning at the hairline in front, extending to the occiput posteriorly and then curving downward and forward toward the ear is made about 2.5 cm. from the midline. The galea and skin are reflected and retracted forward. A bone flap equal in area to this exposure is cut away with a bone-cutting instrument, except over about a third of the longitudinal extent near the midline. The bone flap is elevated and broken at this uncut line, but the break is not complete; it leaves a hinge with good fixation. The bone is now raised about 3 cm. on this fixed hinge but is free elsewhere. The dura is opened parallel to the cut margin of the bone, except along the midline. The brain then promptly bulges to fill the space formed by the elevated bone. To fix the elevated bone flap a piece of bone is cut from the posterior margin of the flap and wired across the defect. After closure of the incision the head is encased in a light plaster cast.

1. King, J. E. J.: Oxycephaly, *Tr. South. S. A.* **54**:8, 1941.

2. Woodhall, B.: Oxycephaly, *J. Pediat.* **20**:585, 1942.

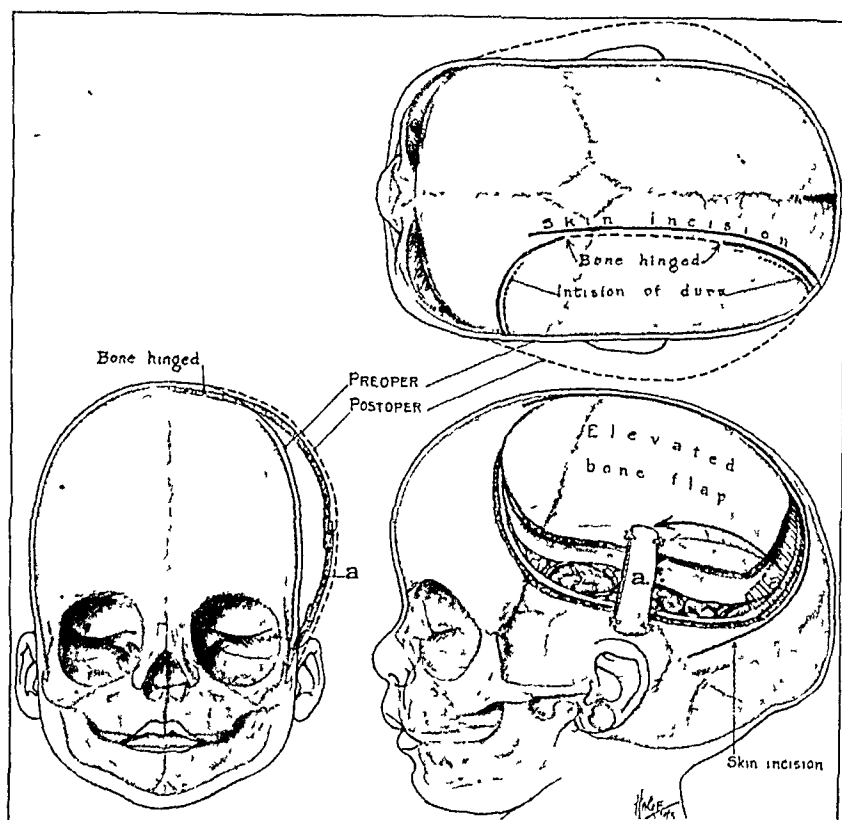


Fig. 1.—Drawing of the operative procedure for correction of scaphocephaly. The narrow head is enlarged by elevating a large bone flap on each side and holding it in position by a transplant of bone (from the bone flap). The dura is incised to allow the brain to expand. The same procedure is carried out on the opposite side two or three weeks later.



Fig. 2.—Ventriculogram showing the long, attenuated ventricles characteristic of scaphocephaly.

The time at which the second side is done can be determined individually. The purpose of the second operation is mainly to produce symmetry of the head, since the intracranial pressure is adequately controlled by the enormous bulge of brain afforded by the decompression of the first operation. In my case the baby was only 5 months old, and an interval of three months was allowed. At the first operation a thin celloidin plate was used and at the second an autotransplant of bone. The latter is probably preferable; it is easily obtained and the loss of bone is negligible. It is worthy of note that a ventricular injection of air was made before operation; the roentgenogram showed that the ventricles were attenuated and elongated to conform to the shape of the narrow scaphocephalic head.

Immediately after the first operation the child became alert, active and responsive and showed a remarkable change from the preoperative listlessness and rather stupid appearance. The baby has since developed normally, and ten months after the first operation is active, bright and seemingly normal in every way. The head is everywhere firm.



Fig. 3.—Photographs taken six months after the first operation showing front and top views of a patient treated by the method described in this article.

Although the long, narrow head of scaphocephaly is more easily transformed into a normally shaped head by this type of operation, than is the pointed, short head of acrocephaly, relief of cerebral symptoms should be secured equally well for either condition.

Whether or not incision of the dura with immediate decompression is essential I do not know. It does no harm and permits immediate filling of the large dead space that would otherwise be left between the dura and the elevated bone. Moreover, a long period must be required for the unopened dura to stretch enough to fill this large space.

My patient is much younger than those of King and of Woodhall. This is an advantage in that early relief of the cerebral compression doubtless prevents permanent stigmas. Then, too, the operative procedure is much simpler because the bone is so thin. It is preferable to operate on the right side first, because the major effects of the cerebral protrusion after the dura is opened are borne by the less actively functioning hemisphere.

SUPPURATIVE ANTERIOR MEDIASTINITIS IN AN INFANT FOLLOWING INTRASTERNAL BLOOD TRANSFUSION

OPERATION AND RECOVERY

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HISTORY OF INTRAMEDULLARY THERAPY

At least as far back as 1903 Wolff¹ practiced marrow puncture on laboratory animals, and in 1910 Ghedini² reported an experience of several years in obtaining specimens of bone marrow from 24 living human patients through puncture holes in the tibia. He recommended the method for the diagnosis of blood dyscrasias without pathognomonic alterations in the circulating blood and for the diagnosis of kala-azar. In 1923 Seyfarth,³ who had been seeking a substitute for splenic puncture in the diagnosis of kala-azar, described his use of a small hand trephine and a platinum wire loop for obtaining specimens of sternal marrow with the patient under local anesthesia. His discovery foreshadowed the observations of Debré and his associates⁴ that sternal puncture in man gives more frequent positive cultures for the diagnosis of septicemia than does venipuncture. In 1928 Sonnenfeld⁵ described a very small trephine modifying Seyfarth's, and it was only a step from this to Arinkin's report⁶ in 1929 of 180 aspirations of sternal marrow, a heavy lumbar puncture needle being used. Sternal puncture became at once a highly popular diagnostic method among hematologists, particularly abroad, and it was natural that the first use of the intramedullary route for administration of therapeutic agents should have been by hematologists. Josefson⁷ in 1934 appears to have been the first of a number of investigators who injected liver preparations into the bone marrow of patients with pernicious anemia. Hoping for direct effect on the marrow, he made over fifty such injections and claimed good results. He used a sternal puncture needle with a collar and set screw as a depth guard and aspirated 4 to 5 cc. of marrow and injected 4 to 5 cc. of liver extract. He discussed the possible extension of the use of intramedullary injections: "Finally I should wish to say that if the intraosseal method is and deserves to be accepted in the future

From the Departments of Surgery and Pediatrics, Johns Hopkins University School of Medicine, and the Harriet Lane Home of the Johns Hopkins Hospital.

1. Wolff, A.: Ueber eine Methode zur Untersuchung des lebenden Knochenmarks von Thieren und über das Bewegungsvermögen der Myelocyten, *Deutsche med. Wchnschr.* **29**:165, 1903.

2. Ghedini, G.: Neue Beiträge zur Diagnostik der Krankheiten der hämatopoetischen Organe mittels Probepunktion des Knochenmarks, *Wien. klin. Wchnschr.* **23**:1840, 1910.

3. Seyfarth, C.: Die Sternumtrepanation, eine einfache Methode zur diagnostischen Entnahme von Knochenmark bei Lebenden, *Deutsche med. Wchnschr.* **49**:180, 1923.

4. Debré, R.; Lamy, M.; Bonnet, H., and Broca, R.: La médulloculture, *Bull. et mém. Soc. méd. d. hôp. de Paris* **51**:1723, 1935.

5. Sonnenfeld, A.: Zur Technik der Sternalpunktion, *Deutsche med. Wchnschr.* **54**:1380, 1928.

6. Arinkin, M. I.: Die intravitale Untersuchungsmethodik des Knochenmarks, *Folia haemat.* **38**:233, 1929.

7. Josefson, A.: A New Method of Treatment: Intraosseal Injections, *Acta med. Scandinav.* **81**:550, 1934.

we will perhaps be able to inject other remedies than campolon [liver extract] in the bone marrow. It is impossible to predict if the intraosseal injection may then be preferred to the intravenous."

A mass of experimental work, chiefly that reported in the French literature, is concerned with intramedullary injections of every conceivable substance.⁸ In the course of this work Benda^{8f} studied the peculiarities of intramedullary injections. He determined that in the guinea pig intramedullary injections of drugs are equivalent to intravenous injections. Roentgenographic studies made with colloidal thorium dioxide showed instantaneous filling of the inferior vena cava and the lungs, and if a soluble iodide was used roentgenograms had to be taken while the injection was still in progress. Air embolism was as easily produced as by direct intravenous injection. Bacteria were as rapidly disseminated as when injected intravenously, and anaphylaxis could be induced as easily by intramedullary injections as by intravenous injections. These observations were confirmed by workers in other French laboratories. More recently the experiments have been repeated in this country.⁹ Bernard^{8h} in 1939 injected colchicine repeatedly into the sternal marrow of a 5 year old boy in a vain effort to affect his leukemia. In July 1940 Henning¹⁰ reported a ten year experience with intrasternal injections of white blood cells for agranulocytosis. Roentgenograms taken with the aid of intrasternally injected iopax and other preparations showed immediate appearance of the material in the mammary veins. He reported the intrasternal administration of drugs, blood and fluids to human beings by means of a sternal puncture needle. For administration of blood, if the flow was too slow, he recommended the use of two needles. He expressed the opinion that his method was particularly adapted to the treatment of peripheral vascular failure with collapse of the peripheral veins. In November 1940 Morrison and Samwick¹¹ reported a single case of aplastic anemia with recovery after intrasternal administration of marrow. The present interest in the intrasternal and other intramedullary routes for administration of blood and fluids was aroused by the publications of Tocantins and O'Neill.¹²

8. (a) Torrey, J. C., and Kahn, M. C.: The Progressive Anemia Following a Single Intramarrow Injection of B. Welchii Toxins, *Am. J. Path.* **5**:117, 1929. (b) Bernard, J.: La stérilité des rats soumis aux injections intra-médullaires de goudron, *Sang* **9**:779, 1935. (c) Codvelle; Bernard, J., and Guichené: Aleucie hémorragique: Essai de traitement par les injections intra-médullaires de goudron, *ibid.* **10**:777, 1936. (d) Tosatti, E.: Lésions myélo-hématiques et stérilité provoquées chez le lapin par les injections intramédullaires de goudron, *ibid.* **10**:388, 1936. (e) Benda, R.: Renseignements fournis par les injections intra-médullaires de sang humaine chez le cobaye, *ibid.* **11**:659, 1937. (f) Benda, R.; Debray, C., and Bourée, J.: Injection du système veineux du cobaye par voie médullaire osseuse: Résultats qu'il est possible d'en attendre, *Bull. et mém. Soc. méd. d. hôp. de Paris* **53**:662, 1937. (g) Bonnet, H.; Dreyfus, B., and Montfiore: Persistance comparée des microbes virulents inoculés au cobaye dans la moelle osseuse et dans le sang circulant, *Compt. rend. Soc. de biol.* **128**:485, 1938. (h) Bernard, J.: Leucémie aiguë: Essai de traitement par les injections intramédullaires de colchicine; modifications médullaires et sanguines, *Sang* **13**:434, 1939.

9 (a) Tocantins, L. M., and O'Neill, J. F.: Infusion of Blood and Other Fluids into the Circulation Via the Bone Marrow, *Proc. Soc. Exper. Biol. & Med.* **45**:782, 1940. (b) Tocantins, L. M.: Rapid Absorption of Substances Injected into the Bone Marrow, *ibid.* **45**:292, 1940.

10. Henning, N.: Die intrasternale Injektion und Transfusion als Ersatz für die intravenösen Methoden, *Deutsche med. Wchnschr.* **66**:737, 1940.

11. Morrison, M., and Samwick, A. A.: Intramedullary (Sternal) Transfusion of Human Bone Marrow: Preliminary Report, *J. A. M. A.* **115**:1708 (Nov. 16) 1940.

12. (a) Tocantins, L. M., and O'Neill, J. F.: Infusion of Blood and Other Fluids into the General Circulation via the Bone Marrow: Technique and Results, *Surg., Gynec. & Obst.* **73**:281, 1941. (b) Tocantins, L. M.; O'Neill, J. F., and Jones, H.: Infusions of Blood and Other Fluids Via the Bone Marrow: Application in Pediatrics, *J. A. M. A.* **117**:1229 (Oct. 11) 1941. (c) Tocantins and O'Neill.^{9a} (d) Tocantins.^{9b}

Intravenous therapy of all sorts, particularly the administration of fluids, blood and plasma, has come to play such a large part in present day therapeutics that the number, size and durability of a patient's veins may actually represent the difference between easy and adequate treatment on the one hand and difficult and inadequate treatment on the other. This observation is especially applicable in a long illness. For this reason the suggestion¹³ that the marrow spaces of the sternum, femur and tibia be used for intravenous infusions seemed to present a solution to the problem of administration of fluids to patients "without veins."

The method has not yet been employed in either the surgical or the pediatric service of this hospital. Not more than 1 or 2 adult patients a year finally reach the point at which intravenous medication is all but impossible; and even for these it is usually possible by recourse to the jugular and the femoral veins to give enough fluid for several days until the more frequently employed superficial veins are once more usable as a consequence of resorption of extravasations, canalization of old thrombi or enlargement of collateral vessels. In the case of infants we have been struck by the fact that superficial veins are always available. Many articles, in journals and in textbooks of medicine and pediatrics, stress the importance of "cutting down" on the veins of infants for giving transfusions of blood. It is the practice in the pediatric service of the Johns Hopkins Hospital to resort to open venesection only for an infusion which is to run uninterruptedly for a number of days. The use of needles of fine bore (up to 27), with administration of the fluid under pressure, makes it possible to give all intravenous treatments, except the "continuous drip," by percutaneous puncture of superficial veins, even those as small as the digital veins of infants; not infrequently a fine needle, snugly taped in place, serves for continuous infusions. Despite the apparent advantages of a method which requires one to strike only the marrow cavity of a bone instead of the lumen of a fragile vein, we have not employed the infusion of fluids into the bone marrow, on the ground that it is an unnecessarily hazardous procedure, which is trying for the patient and which, on the basis of the figures supplied by the proponents of the method, will not deliver quantities of fluid with sufficient rapidity to justify its use.¹⁴ The method requires special skill and experience, which are to be gained only from constant use, but its use without the special indications which exist only in occasional cases is not justifiable.

It is worth noting that in the case reported hereinafter, an intramedullary transfusion was attempted in one hospital, with serious consequences. Subsequently in the same hospital as well as in the Harriet Lane Home after the baby was transferred, although she was then edematous and almost moribund, no difficulty was encountered in giving blood and fluids at will by percutaneous puncture through veins of the scalp and the extremities. In fairness to Tocantins and O'Neill and other advocates of intramedullary transfusion, it must be pointed out that the statement that "in a child under 3 years of age, the marrow in the sternum is probably not developed to the point that it will allow this site to be used"^{12a} was

13. Henning.¹⁰ Tocantins and O'Neill.^{12a} Tocantins, O'Neill and Jones.^{12b} Tocantins, L. M.; O'Neill, J. F., and Price, A. H.: Infusions of Blood and Other Fluids Via the Bone Marrow in Traumatic Shock and Other Forms of Peripheral Circulatory Failure, *Ann. Surg.* **114**:1085, 1941.

14. The average rate of flow in the manubrium^{12b} is 3.4 cc. a minute; in the body of the sternum, 3.1 cc. a minute, and in the tibia or femur of children, 1.7 cc. a minute. That is to say, according to these averages, it would require two and one-fourth hours to administer 500 cc. of blood to an adult; thus the use of intramedullary injections is precluded in an emergency unless the fluid is to be forced in by syringe. When this method was used a maximum rate of 57.5 cc. a minute was attained in 1 case.

disregarded. The special needle devised by Tocantins and O'Neill was not employed; but since sternal puncture is a familiar procedure and needles for its performance are in general use, one may expect, as reports are beginning to show,¹⁵ that sternal puncture needles of varying design will be used for this new purpose. In the present instance, since there is nothing to indicate that the child had an infection of the blood stream before or after transfusion, the appearance of pus in the mediastinal extravasation suggests that the blood may have been contaminated. A few organisms introduced into a vein, and probably into the bone marrow, are ordinarily of no consequence.¹⁶ In the mediastinum the results can be extremely serious. There is already one report in the literature¹⁷ regarding the fatal effects of intrapleural administration of a large infusion of dextrose meant for the sternum. An autopsy was not done, and the status of the mediastinum was not known. The infusion was given during an elective operation, and death followed.

SUPPURATIVE ANTERIOR MEDIASTINITIS

Most discussions of mediastinitis deal with infections of the posterior mediastinum. Posterior mediastinitis results from esophageal or tracheal perforation, disease of the tracheobronchial lymph nodes, diseases of the lungs or the pleura, and extension from cervical infections. Furstenberg¹⁸ has clearly demonstrated that the attachment of both the superficial fascia and the anterior layer of the pre-tracheal fascia to the under side of the manubrium prevents the spread of cervical infection into the anterior mediastinum. Nevertheless, Neuhoff and Jemerin¹⁹ reported the case of a 9 month old infant who had an anterior mediastinal abscess in direct continuity with a cervical abscess. These authors reported a number of severe thoracic infections, usually associated with posterior mediastinitis, which finally involved the anterior mediastinum. However, these are exceptions. Cervical and posterior mediastinal infections rarely involve the anterior mediastinum, and anterior mediastinitis is in consequence an uncommon condition. A number of cases of alleged anterior mediastinal abscess in the literature are probably posterior mediastinal abscesses extending far anteriorly and displacing the soft tissues before them. Such a case is described by Neuhoff and Jemerin. A number of anterior mediastinal abscesses following simple fracture of the sternum have been described.²⁰ Acute hematogenous osteomyelitis of the sternum may cause acute suppurative anterior mediastinitis.²¹

The most important specific symptoms of acute suppurative anterior mediastinitis are edema of the head and arms with venous distention in the same region,

15. Gomez, E.; Collar, A., and Calderin, C.: Transmédula-ósea infusión, *Rev. de med. y cir. Habana* **47**:113, 1942.

16. However, Bonnet and his associates found in experimental septicemia that organisms remained in the blood stream eleven to fifteen days under their experimental conditions, but in the bone marrow twenty-one days. In the presence of trauma to the sternum, osteomyelitis might be expected to result in some cases.

17. Papper, E. M.: Bone Marrow Route for Injecting Fluids and Drugs into the General Circulation, *Anesthesiology* **3**:307, 1942.

18. Furstenberg, A. C.: Acute Mediastinal Suppuration, *Tr. Am. Laryng., Rhin. & Otol. Soc.* **35**:210, 1929.

19. Neuhoff, H., and Jemerin, E. C.: Acute Infections of the Mediastinum, Baltimore, Williams & Wilkins Company, 1943.

20. McKinlay, C. A.; Kinsella, T. J., and Radl, R. B.: Acute Essential Hypertension Precipitated by Mediastinal Abscess, *Arch. Int. Med.* **54**:645 (Oct.) 1934.

21. Perras, T.: Beitrag zur Chirurgie des Brustbeins und des Mittelfelles, *Deutsche Ztschr. f. Chir.* **254**:246, 1940.

and dyspnea. Lezius²² made the point that in anterior mediastinitis the dyspnea is inspiratory and in posterior mediastinitis expiratory and that cyanosis is more apt to occur in the latter. Lezius as well as McKinlay, Kinsella and Radl²⁰ noted acute hypertension, which was also present in our patient. All authors agreed on the necessity for early resection of portions of the ribs or sternum or both.

REPORT OF A CASE

J. B., a Negro girl aged 8 months, was transferred to the Harriet Lane Home of the Johns Hopkins Hospital on Oct. 9, 1942, for surgical consultation because of complications following an intrasternal blood transfusion. Fever, dyspnea, edema of the face and arms and broadening of the mediastinal shadow were present. In May 1942, at the age of 3 months, she had been followed in the Harriet Lane Dispensary for one week because of acute nutritional disturbance, associated with otitis media and infection of the upper part of the respiratory tract. She was treated with sulfathiazole for five days, during which her temperature dropped from 104.2 to 98.6 F. and her symptoms subsided. The hemoglobin content of the blood was 10.5 Gm. per hundred cubic centimeters, and the white cell count was 5,000 to 8,000.

In July 1942, at the age of 5 months, the patient was admitted to the infants' ward of the Harriet Lane Home with a similar but more severe attack complicated by pneumonia in the upper lobe of the right lung. The hemoglobin content of the blood was 8.5 Gm. per hundred cubic centimeters. Nasopharyngeal cultures grew a type VII pneumococcus. Sulfathiazole therapy was started. Two days later the hemoglobin content of the blood was only 5.0 Gm. per hundred cubic centimeters. There was no sickling of the red blood cells. After three transfusions totaling 290 cc. of blood the hemoglobin content had risen to 12.0 Gm. She returned two weeks later with a history of diarrhea, fever and infection of the upper portion of the respiratory tract of five days' duration. This illness continued for three weeks. Pallor, cardiac enlargement, hepatomegaly and dyspnea developed, and she was admitted to another hospital, since no beds were available in the Harriet Lane Home. She stayed there for ten days and received 210 cc. of blood, which raised her hemoglobin content from 4.6 to 11.6 Gm. per hundred cubic centimeters.

On September 26 she returned to the Harriet Lane Home, with fever and vomiting. She was pale, and her heart was enlarged and was beating rapidly and overactively. The liver was palpable 1 fingerbreadth below the costal margin. The hemoglobin content of the blood was 4 Gm. per hundred cubic centimeters, and the red cells, as before, did not sickle. The wards in the Harriet Lane Home being full, she was again admitted to the other hospital.

On admission there she was described as being pale and listless. The skin was dry; there were no palpable glands; the tonsils were moderately enlarged, and the lungs were clear on auscultation and to percussion. The heart was moderately enlarged to the left, but the sounds were of good quality; the rate was rapid and the rhythm regular, and there were no murmurs. The liver was palpable 1 fingerbreadth below the costal margin; the spleen was not palpable. The urine was normal. The white cell count was 4,700 with 28 per cent polymorphonuclears and 72 per cent lymphocytes. The hemoglobin content was 4.8 Gm. per hundred cubic centimeters. Twenty cubic centimeters of whole blood was injected into one buttock.

On September 28 the hemoglobin content of the blood was 4.4 Gm. per hundred cubic centimeters and the red cell count was 1,040,000. The child was afebrile, but her condition was unchanged. On September 29 she was given intravenously 100 cc. of matched citrated blood which had been drawn on September 25. The bottle was recapped and placed in the ward's electric refrigerator. The transfusion was followed by a slight rise of temperature, but there was no chill. On September 30 the hemoglobin was 8.2 Gm.

On October 1 puncture of the sternal marrow was attempted, and marrow is said to have been obtained. The needle was described as a 16 gage sternal puncture needle. With the needle in place it was decided to administer blood intrasternally. Accordingly 75 cc. of the same blood which had been given on September 29 was given by gravity through the sternal puncture needle. After this the patient's temperature slowly rose to 104.0 F. and remained almost constantly at that level thereafter. It was noticed then that she was becoming progressively more edematous and that her face was disproportionately swollen. The liver remained palpably enlarged.

On October 2 the administration of mersalyl and theophylline produced slight reduction in the edema. On October 3 the hemoglobin content of the blood was 5.8 Gm. per hundred cubic

22. Lezius, A.: Die Behandlung der akuten eitrigen Mittelfellentzündung, *Arch. f. klin. Chir.* 196:616, 1939.

centimeters. A transfusion of 60 cc. of blood into a vein of the scalp on October 6 was without incident.

On October 2 a roentgenogram of the heart (fig. 1 *A*) showed that the cardiac shadow was enlarged, especially at the base. One on October 6 (fig. 1 *B*) showed a considerable increase in the cardiac shadow which was much more pronounced over the base than in the area of the ventricles. The edema of the face became more striking, and the patient lay with her head thrown back. Sulfathiazole and digitalis, administration of which was started on October 6, had had no perceptible effect, and on October 9 the baby was transferred to the Harriet Lane Home for consideration of surgical intervention.

On admission her pulse was 180, her respirations 60 and her blood pressure 112 systolic and 84 diastolic. She was a well nourished infant, strikingly pale and with an extreme degree of facial edema. She appeared mortally ill. Dyspnea was severe. The head was held retracted, but the neck was not stiff. She had a spasmodic, paroxysmal, slightly brassy cough. The edema, which was most pronounced around the eyes and lips, extended to both upper extremities, and there was some pitting over the upper part of the thorax, particularly behind. There was a puncture wound over the center of the sternum, which was entirely covered with a bluish subcutaneous discoloration. The contour of the chest was peculiar, with an anteroposterior fulness.

She was seen by Dr. Helen B. Taussig, who made the following note: The heart seemed definitely enlarged. The retromanubrial dulness was increased and there was dulness over the

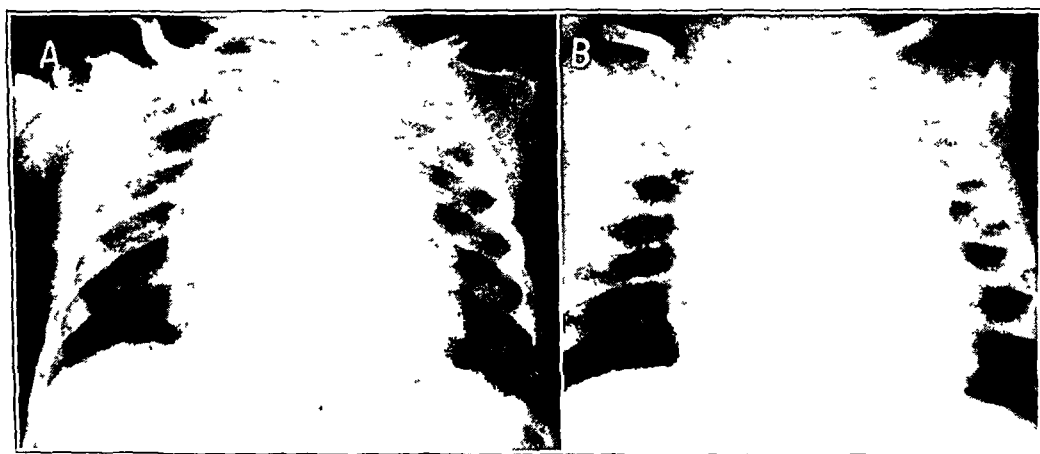


Fig. 1.—*A*, Oct. 2, 1942: enlargement of the cardiac shadow, particularly at the base. *B*, Oct. 6, 1942: increase in the mediastinal shadow.

left upper lobe continuous with it. The apex beat was felt in the anterior axillary line. The heart sounds were well heard and forceful in the axilla but were distant over the precordium itself. There was a striking discrepancy between the ease with which they were heard in the axilla and their muffled quality over the heart. There were no endocardial murmurs. The liver was slightly enlarged. Under the fluoroscope the heart shadows were hazy. The mediastinal shadow was wide, and it was difficult to make out the cardiac pulsation in the anteroposterior view. In the left anterior oblique position it was striking that there was a strong pulsation posteriorly in the region of the left ventricle and absence of pulsation anteriorly over the right ventricle, and that there was a wide mediastinal shadow which fused with the cardiac border and did not pulsate. In the right anterior oblique position the esophagogram was essentially normal, and in the anteroposterior position the esophagus seemed to deviate slightly to the left and then descended normally.

The red blood cell count was 1,670,000, the hemoglobin content 4.0 Gm per hundred cubic centimeters and the white blood cell count 4,100, with 85 per cent lymphocytes. The non-protein nitrogen content of the blood was 19 mg. per hundred cubic centimeters and the carbon dioxide-combining power was 64 volumes per cent. The total protein content was 5.2 Gm. per hundred cubic centimeters, the albumin content of the serum 3.1 Gm and the globulin 2.1 Gm. The chloride content was 105 mg. per hundred cubic centimeters. The van den Bergh test showed 4.7 mg. of bilirubin per hundred cubic centimeters of serum.

There was by now general agreement that the patient presented the picture of obstruction to the superior vena cava due to the introduction of blood into the anterior mediastinum, where

under the fluoroscope a mass could be plainly seen. It was thought that the moderate hypoproteinemia which was present permitted the rapid appearance of edema.

There was some dispute as to whether there was merely a collection of blood, which could be trusted to resorb in time, or an actual abscess. This question was resolved by aspiration in the third interspace parasternally, which was the area of maximum dullness to percussion; with the needle angled toward the mediastinum the first puncture yielded 2 or 3 cc. of thick, reddish brown pus. Microscopic examination of the pus showed numerous fresh and partly autolyzed white blood cells and old, clumped red blood cells, some of which were in rouleau formation. Gram stain showed numerous polymorphonuclears and many gram-negative rods which proved on culture to be *Escherichia coli*.



Fig. 2.—Nov. 30, 1942: small unhealed granulating wound.



Fig. 3.—A, Nov. 18, 1942: some persistence of increase in the breadth of the mediastinal shadow as compared with B. B, July 19, 1942: narrower mediastinum at the time of the previous admission, when the patient had pneumonia.

Operation was undertaken on the day of admission with the patient under local anesthesia. A curved incision was made over the left side of the sternum and carried with difficulty through the edematous tissues down to the bone. At this point there was discharge of thin, dirty brown pus. The edge of the sternum and a neighboring costal cartilage, probably the third, were carefully rongeured away until a definite abscess cavity was exposed just behind the left border of the sternum and sufficiently large to admit one's index finger. The surrounding tissues were the seat of an intense cellulitis and exuded a dark brownish fluid; only in the small abscess cavity itself was there any thick, well formed pus, the fluid in the area involved by mediastinal cellulitis being thin. A little sulfanilamide powder was dusted into the wound, which was drained and lightly packed.

After operation the patient was given an intravenous transfusion of 100 cc. of blood, and treatment with sulfathiazole was begun. A continuous intravenous drip of blood was started

the next day, October 10, through which she received 145 cc. of blood, and on October 11, 200 cc. was given. On October 12 the edema of the face was greatly increased, she was unable to open her eyes and her hands and arms were edematous. The pulse was rapid and thready, and the temperature was still constantly elevated. Although the child had been lying with the head higher than the feet, no edema of the feet or ankles had developed.

On October 13 the edema began to subside, the pulse became stronger and slower and the temperature began to fall. The edema regressed slowly, so that it was almost gone by October 23 and completely gone by October 30. On admission her weight had been 7.04 Kg., but it dropped, with subsidence of edema, to 6.6 Kg. on October 14 and to 5.82 Kg. on October 21. Thereafter it slowly increased without recurrence of the edema. Administration of sulfathiazole was continued until November 7. At discharge, on November 30, she was afebrile, bright and cheerful, and the amount of hemoglobin in the blood was slowly rising without the aid of transfusions and had reached 10.0 Gm. per hundred cubic centimeters, with 3,270,000 red blood cells. The wound was all but healed (fig. 2). Comparison of roentgenograms taken two weeks before her discharge from the hospital (fig. 3 *A*) with those taken during her previous admission, when she had pneumonia of the right upper lobe (fig. 3 *B*), reveals some persistent widening of the mediastinum.

A final examination on April 30, 1943, revealed her to be well and vigorous. Her heart was not enlarged. Her blood pressure was consistently within normal limits (90 systolic and 60 diastolic). Under the fluoroscope the mediastinum was seen to be no longer widened and all cardiac pulsations were plainly visible.

SUMMARY

Suppurative mediastinitis in an infant of 8 months followed attempted intra-sternal transfusion of blood through a needle inserted for the purpose of making a sternal puncture. The blood had been drawn six days previously and had been used two days before for an intravenous transfusion in the same child.

Fever, dyspnea and obstruction to the venous return from the head, chest and arms, manifested by pronounced edema, were the chief responses to the lesion. The head was held retracted and there was hypertension. Fluoroscopic examination showed a mass in the anterior mediastinum, overlying chiefly the base of the right ventricle.

Aspiration of the mediastinum yielded pus, and recovery followed resection of the overlying sternum and costal cartilage, with drainage of the abscess and of the diffuse mediastinitis.

THERAPY OF SHOCK IN EXPERIMENTAL ANIMALS WITH PLASMA AND SERUM PROTEIN SOLUTIONS

III. FREEZING SHOCK: CONCENTRATED PLASMA AND SERUM THERAPY WITH AND WITHOUT AMPUTATION OF THE DAMAGED EXTREMITY

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Freezing of one hindlimb of a dog has been demonstrated by studies carried out after thawing¹ to result in damage to the tissues and capillaries of the frozen site involving the skin, subcutaneous tissues and muscles down to the bones and leading to a lowered plasma volume and fatal shock. It was also observed that a greater portion of the loss in volume of the circulating plasma occurred during the first three hours after the freeze, at which time microscopic evidence of generalized visceral cellular damage and capillary dilatation (atony) was minimal or absent.² The interval between the third and the fourth hour was observed to be the borderline period beyond which generalized visceral capillary stasis and parenchymatous damage became pronounced.

When no therapy was instituted these animals¹ usually died in shock about eight hours after the freeze. In addition, it was observed³ that a severe arterial hypotension occurred late, and that once this symptom appeared the complete reestablishment of the plasma volume delayed the onset of a fatal termination but did not avert it. It was therefore considered appropriate to study the effects of the following three therapeutic procedures conducted between three and three-tenths and four and eight-tenths hours after the freeze, during the borderline period of advanced generalized visceral changes.

Three groups of experiments with 10 dogs each were conducted. In the first group the damaged limb was amputated between three and two-tenths and three and nine-tenths hours (average) after the freeze was terminated, and no intravenous protein therapy was instituted. The second group received adequate intravenous protein therapy in concentrated form between four and two-tenths and four and nine-tenths hours (average), and the damaged limb was left intact. In the third group the damaged limb was amputated between three and three-tenths and three and ninety-nine hundredths hours and adequate intravenous protein therapy (concentrated) was instituted between four and three-tenths and four and eight-tenths hours (average).

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1. Muirhead, E. E.; Ashworth, C. T.; Kregel, L. A., and Hill, J. M.: Experimental Freezing Shock: I. Changes in Body Fluids and Tissues, *Arch. Surg.* **45**:863-889 (Dec.) 1942.

2. The time element of three hours is related strictly to severe freeze of one hindlimb. Bilateral freezing considerably accelerated the depletion of plasma volume.

3. Muirhead, E. E.; Ashworth, C. T.; Kregel, L. A., and Hill, J. M.: The Therapy of Shock in Experimental Animals with Serum Protein Solutions: II. Fate in the Body of Concentrated and Dilute Serum and Saline Solutions, *Surgery* **14**:171-190 (Aug.) 1943.

METHODS

Healthy dogs were chosen, and before freezing was begun anesthesia was induced with pentobarbital sodium⁴ in doses usually of 1 grain (0.06 Gm.) for every 5 pounds (2.3 Kg.) of body weight. The freezing procedure has been described.¹ The fur of one extremity was closely clipped, and care was taken to stop the freeze at the level of the inguinal ligament by padding the lower part of the abdomen and external genitalia with cloth and cotton and wrapping a rubber sheet around the dog over this insulating material. After the freeze the limb was allowed to thaw at room temperature. When the animals awakened, pain was relieved by appropriate doses of dilaudid given subcutaneously, but except for the original anesthesia the animals were kept just below the pain threshold. No analgesics were given beyond four hours postoperatively.

With proper surgical technic a guillotine type of amputation with disarticulation of the knee joint was performed. The sciatic nerve was severed first after the cutaneous incision, since tugging of this nerve precipitated extreme restlessness. Care was taken to keep bleeding at a minimum. After the amputation the wound was coated with sulfanilamide powder and the edges of the skin were approximated with interrupted mattress sutures. This procedure resulted in an oblique linear wound. Four preliminary amputations were performed to establish the technic, and subsequently experiments in various groups were alternated, starting with 2 dogs in group 3. The dogs in the latter group received plasma after the operation.

The batches of concentrated plasma and serum contained an average of 18.2 Gm. of proteins (albumin and globulin) per hundred cubic centimeters. These solutions were injected by means of 50 cc. syringes into the jugular vein. When the entire interval is taken for the injection the average rate was 0.2 cc. per minute per kilogram of body weight (average of 100 cc. given in forty minutes to dogs weighing an average of 12 Kg.). We wish to stress, however, that the doses were injected intermittently. Usually 5 to 10 cc. was injected in ten to thirty seconds, with an interval of one and five-tenths to two minutes between doses. On occasions the injections were made at slower rates, as will be explained hereinafter. In these experiments the intervals between injections were chosen for a dual purpose. Time was allowed for the excess sodium citrate in the plasma to be oxidized, its transient binding effect on the calcium in the circulating plasma being considerably reduced. Time was also allowed for accommodation of the circulatory system to the effects of the concentrated solutions, including a sudden increase in plasma volume resulting from the transfer of tissue fluids into the blood stream and the increase in the venous return to the heart of red blood cells.³

A sample from each injected dose of concentrated plasma and serum was taken for a protein determination in order that the exact number of grams of protein given each animal could be determined. The doses of protein given had been previously observed³ to effect an adequate replacement of the plasma volume and circulating proteins for dogs of this size.

Human plasma and serum⁵ prepared by the pooling of bloods technic⁶ were used. The plasma was obtained from citrated blood and was desiccated by the adtevac process.⁷ Usually

4. The pentobarbital sodium was furnished by Abbott Laboratories, North Chicago, Ill.

5. Before the present experiments we had not observed reactions to agglutinin-free human plasma in dogs other than reactions attributable to citrate, i. e., transient tetany, and reactions discussed later in the text as "transient depressor effect." Urticaria has been observed by others (Ashworth, C. T.: Unpublished data), but we did not encounter it in these experiments. During a more recent group of experiments¹⁶ on dogs occasional changes in blood pressure of anaphylactoid type were observed following small doses of normal or concentrated human plasma. Only a few dogs responded in this manner, and no anaphylactoid fatalities have been encountered. The arterial pressure dropped gradually to levels around 50 mm. of mercury and returned to normal within twenty to forty minutes. When the recovery occurred, doses of the same batch of plasma similar to the original one or larger failed to initiate a similar depressor effect. These anaphylactoid manifestations were altogether different from the depressor effect referred to later. The fact that all animals in group 3 completely recovered, while those in group 2 died in shock, seems to support the deduction that anaphylactoid phenomena did not influence the present results.

6. Hill, J. M., and Muirhead, E. E.: Desiccated Plasma for National Defense: Mass Production Methods Based on the Adtevac Process, *J. Lab. & Clin. Med.* **27**:812-819 (March) 1942.

7. Hill, J. M., and Pfeiffer, D. C.: A New and Economical Desiccating Process Suitable for the Preparation of Concentrated Plasma or Serum for Intravenous Use: The Adtevac Process, *Ann. Int. Med.* **14**:201-214 (Aug.) 1940.

15 Gm. of the dry product was dissolved in 45 cc. of solvent (water and dilute citric acid solution).

Samples of venous blood were collected from an exposed jugular vein without hemostasis for duplicate determinations of the hemoglobin concentration (Sanford-Sheard photoelectric method⁸) and the plasma protein concentration (Greenberg method⁹). The mean carotid arterial pressure was taken with a mercury manometer with 2.5 per cent sodium citrate solution in the system. The control procedures were performed before the freeze and immediately after the onset of pentobarbital sodium anesthesia.

The wounds in the neck exposing the carotid artery and jugular vein were closed after the application of sulfanilamide powder.

The animals were kept at room temperature. Those which survived were allowed to drink water ad libitum fourteen to sixteen hours after the operation. The subsequent diet consisted of dog biscuits and ground meat.

Autopsies were performed on 21 animals (7 from each group), and representative samples of tissue were obtained from the viscera, the thawed limb, the amputation site and the remote somatic musculature for microscopic study with the routine hematoxylin-eosin stain. This procedure was conducted shortly after death. The protein concentration of the edema fluid in the thawed limb was determined in 7 animals.

RESULTS

All of the 30 animals in the three groups displayed a degree of venous hemoconcentration after three to four and two-tenths hours which according to previous studies¹ accounted for 75 to 85 per cent of the loss in plasma volume necessary to produce fatal shock by this procedure (severe freeze). The average plasma protein concentration during this period was slightly increased, partly as a result of hemoglobinemia. The mean arterial pressure either was slightly elevated or remained unchanged.

All of the observations up to this time (three to four and two-tenths hours) corroborated previous studies.¹ Since a similar procedure (severe freeze) was previously observed always to end fatally, any success in averting a fatal outcome is taken to be the result of the therapeutic measures instituted. With this reasoning in mind the results will be analyzed.

I. AMPUTATION; NO PROTEIN THERAPY (TABLE 1)

Five of the 10 animals died within twelve hours after the amputation. The appearance of the tissues was the same as that found after death from shock without amputation. Three dogs died one to two weeks later in a state of extreme anemia and hypoproteinemia without evidence of gross hemorrhage from the operative site. Two dogs lived and subsequently appeared healthy.

The average mean arterial pressure fifty-four minutes after the operation was 18 mm. of mercury lower than the control level. No instance of severe hypotension was encountered up to this time. The venous hemoglobin was usually slightly lowered after the operation. The plasma protein concentration was lowered by an average of 0.62 Gm. per hundred cubic centimeters. These changes probably resulted from loss of blood during the operation.

The histopathologic findings for each group are discussed under a separate heading below.

II. PROTEIN THERAPY; NO AMPUTATION (TABLE 2)

Eight of the 10 animals died twelve to twenty hours after the concentrated protein therapy. The appearance of the tissues was likewise that observed in

8. Sanford, A. H., and Sheard, C.: The Determination of Hemoglobin with the Photoelectrometer, *J. Lab. & Clin. Med.* **15**:483-489 (Jan.) 1930.

9. Greenberg, D. M.: The Colorimetric Determination of the Serum Proteins, *J. Biol. Chem.* **82**:545-550 (May) 1929.

animals dying in shock. The limb which had been frozen and thawed was found to be markedly swollen, much larger than in animals who had died in shock without therapy.¹ The edema was present throughout the limb but was most pronounced in the subcutaneous region.

Two animals died seven and nine days later after remaining drowsy and stuporous and displaying a recurrence of hemoconcentration. The damaged limb was gangrenous and infected.

The mean arterial pressure at the time of therapy (average four and two-tenths hours after the freeze) was in the normal range (average 152.4) and after

TABLE 1.—*Amputation—No Protein Therapy*

Dog	Weight, Kg.	Time of Amputation, Hours After Termination of Freezing	Interval	Blood Pressure, Mm. of Mercury	Venous Hemo-globin, Gm. per 100 Cc.	Plasma Protein Concentration, Gm. per 100 Cc.	Comments
1	13	3.5-4.5	Control..... 2.75 hr..... 20 min. after operation	155 170 135	14.45 20.0 19.9	Died within 10 to 12 hr.
2	14.5	3.1-4.25	Control..... 2.75 hr..... 40 min. after operation	173 158 155	13.85 19.63 19.15	6.96 7.68 6.24	Lived 2 mo.; killed; hemoglobin, 15.85, 14.7, 12.95; serum protein, 6.16, 6.12, 7.16
3	12.5	3.3-4.3	Control..... 3.1 hr..... 1.1 hr. after operation	158 170 120	12.0 17.0 16.4	6.9 7.2 7.28	Died in 4 hr.
4	17.1	3.1-4.1	Control..... 3 hr..... 1.1 hr. after operation	135 160 142	14.45 19.15 19.4	7.36 7.72 7.2	Died within 10 to 12 hr.
5	11.3	3.1-3.75	Control..... 3 hr..... 2.25 hr. after operation	158 165 135	15.0 19.7 19.15	6.72 7.28 7.22	Died 14 days later with anemia, hypoproteinemia *
6	9	3.2-3.75	Control..... 3.1 hr..... 10 min. after operation	160 120 95	12.95 17.0 16.2	5.56 7.16 5.9	Died 8 days later with anemia, hypoproteinemia *
7	7.1	3.1-3.3	Control..... 3 hr..... 1.1 hr. after operation	148 135 102	10.4 17.15 16.7 7.93 7.08	Died within 10 to 12 hr.
8	98	3.5-3.9	Control..... 3.3 hr..... 18 min. after operation	158 165 142	13.25 19.0 19.15	6.4 7.12 6.85	Died within 10 to 12 hr.
9	6	3.2-3.6	Control..... 3.1 hr..... 1.1 hr. after operation	105 130 105	12.65 17.5 16.5	5.64 6.04 5.26	Lived
10	9.8	3.5-3.9	Control..... 3.5 hr..... 32 min. after operation	130 160 102	12.3 17.15 16.65	6.16 6.4 6.0	Died 10 days later with bronchopneumonia and shock picture
Average 11		3.26-3.93	Control..... 3 hr..... 54 min. after operation	148 153.3 122.3	13.13 18.33 17.92	6.46 7.18 6.56	5 dogs died in shock; 3 dogs died 8 to 14 days later with anemia and hypoproteinemia; 2 dogs lived

* Hemoglobin level 3.4 and 3.7 Gm. per hundred cubic centimeters; plasma protein concentration 4.1 and 4.4 Gm. per hundred cubic centimeters.

therapy (average thirty-six minutes) fell slightly (average 142.8). The plasma protein concentration of the recipient was lowered after therapy by an average of 0.33 Gm. per hundred cubic centimeters. Since a concentrated protein solution of three to three and five-tenths times normal concentration was given, the lack of elevation of the concentration of protein in the recipient's circulating plasma is interpreted as indicating the entrance of fluid into it. This reasoning is further supported by the lowering of the concentration of hemoglobin in the venous blood. The latter was not lowered to the control level as one would expect it to be after an adequate replacement of the plasma volume. This feature has been observed previously³ and will be discussed later.

III. AMPUTATION; PROTEIN THERAPY (TABLE 3)

All of the 10 animals lived and appeared healthy subsequently. These animals were killed an average of twenty-eight days after the operation. Postmortem examination revealed no abnormality of the viscera.

The day after the operation half of the animals displayed a decrease in venous hemoglobin of 1.0 to 2.5 Gm. per hundred cubic centimeters below the control

TABLE 2.—*Protein Therapy—No Amputation*

Dog	Weight, Kg.	Time of Therapy, Hours After Termination of Freezing	Interval	Blood Pressure, Mm. of Mercury	Venous Hemo-globin, Gm. per 100 Cc.	Plasma Protein Concentration, Gm. per 100 Cc.	Comments
1	14.3	4.3-5	Control.....	158	13.85	5.8	Concentrated human plasma, 87 cc. = 19.7 Gm. protein; died within 12 hr.
			4.2 hr.....	105	19.9	8.16	
			30 min. after therapy	120	18.15	7.72	
2	13.7	4.6-5.3	Control.....	162	14.15	5.73	Concentrated human plasma, 119 cc. = 21.8 Gm. protein; died within 12 hr.
			4.6 hr.....	200	21.65	6.96	
			38 min. after therapy	165	19.7	6.56	
3	11.5	4.3-5	Control.....	140	13.85	5.64	Concentrated human plasma, 99 cc. = 18 Gm. protein; died within 12 hr.
			4.3 hr.....	150	18.65	6.24	
			35 min. after therapy	100	15.55	5.92	
4	4-4.5	Control.....	112	11.3	4.82	Concentrated human plasma, 131 cc. = 21 Gm. protein; died within 12 hr.
			4 hr.....	132	18.15	6.0	
			33 min. after therapy	135	15.8	6.12	
5	10.6	4-4.5	Control.....	143	13.4	Concentrated human plasma, 101 cc. = 18.5 Gm. protein; died within 20 hr.
			4 hr.....	145	23.0	7.32	
			1.1 hr. after therapy	132	20.65	7.28	
6	15	4-4.8	Control.....	175	13.25	Concentrated human plasma, 169 cc. = 19.5 Gm. protein; died within 18 hr.
			4 hr.....	155	22.7	8.0	
			53 min. after therapy	154	21.15	6.52	
7	19.4	4.8-5.4	Control.....	175	12.65	7.2	Concentrated human plasma, 115 cc. = 19.7 Gm. protein; next day hemoglobin, 17.15; protein, 7.28; died 7 days after therapy
			4.8 hr.....	125	18.15	7.68	
			16 min. after therapy	135	14.7	7.2	
8	13.6	4-4.7	Control.....	165	13.85	5.56	Concentrated human plasma, 112 cc. = 19.1 Gm. protein; died within 12 hr.
			4 hr.....	200	19.4	6.48	
			42 min. after therapy	190	15.85	6.52	
9	10.7	4-5	Control.....	152	13.85	5.64	Concentrated human plasma, 110 cc. = 17.9 Gm. protein; died within 12 hr.
			4 hr.....	160	21.0	6.56	
			31 min. after therapy	152	18.4	6.43	
10	17	4-4.7	Control.....	165	15.55	6.14	Concentrated human plasma and canine serum; 126 cc. = 21.3 Gm. protein; died 9 days later
			4 hr.....	152	21.3	6.8	
			15 min. after therapy	145	19.1	6.6	
Average	13.97	4.2-4.89	Control.....	154.7	13.57	5.81	Concentrated human plasma, 110.9 cc. = 19.6 Gm. protein; 8 died in shock; 2 died 7 to 9 days later from gangrene and shock
			4.19 hr.....	152.4	20.39	7.01	
			36.3 min. after therapy	142.8	17.9	6.68	

level and in the other animals the venous hemoglobin was almost the same as the control level. In 4 animals the concentration of protein in the plasma was lowered by an average of 1.0 Gm. per hundred cubic centimeters the day after the operation. At the time the animals were killed, the plasma protein concentration was near or slightly above the control level and the hemoglobin concentration was slightly below the control.

The surgical wound healed well. The upper three fourths of the wound healed by primary intention. Usually the lower fourth, opposite the protuberance by

the ischium, dehiscence and healed by means of a granulating surface. Occasionally a small zone of infection developed in the skin, but these areas were readily controlled. No instance of complete wound dehiscence or of widespread infection was observed.

Usually a slight decrease in the venous hemoglobin concentration and plasma protein concentration occurred after the operation and prior to plasma therapy.

TABLE 3.—*Amputation and Protein Therapy*

Dog	Weight, Kg.	Time of Amputation, Hours After Termination of Freezing	Time of Therapy, Hours After Termination of Freezing	Interval	Blood Pressure, Mm. of Mercury	Venous Hemo-globin, Gm. per 100 Cc.	Plasma Protein Concentration, Gm. per 100 Cc.	Comments
1	7.2	2.9-3.6	4-4.5	Control.....	130	10.4	Concentrated human
				2.9 hr.....	120	15.3	serum, 95 cc. = 16.5
				4 hr.....	95	14.45	Gm. protein; lived
				14 min. after therapy	130	9.5	
2	10.3	3-4	4.23-4.8	Control.....	130	13.7	Concentrated human
				3 hr.....	140	20.0	serum, 90 cc. = 16.4
				4.1 hr.....	125	20.15	Gm. protein; lived
				48 min. after therapy	125	15.0	
3	11	3.1-4	4.25-4.83	Control.....	135	13.25	6.48	Concentrated human
				3 hr.....	160	20.65	6.2	serum, 76 cc. = 14.3
				4.1 hr.....	130	19.5	7.2	Gm. protein; lived
				33 min. after therapy	125	15.4	6.9	
4	12.5	3.3-4.3	4.35-5	Control.....	158	14.8	7.28	Concentrated human
				3.1 hr.....	150	22.15	7.24	plasma, 83 cc. = 17.4
				4.3 hr.....	118	21.9	6.94	Gm. protein; lived
				30 min. after therapy	134	18.5	7.04	
5	9.1	3.1-3.9	4.5-5.1	Control.....	140	16.5	7.04	Concentrated human
				3.1 hr.....	168	20.9	7.58	plasma, 83 cc. = 17.7
				4.5 hr.....	125	20.15	Gm. protein; lived
				15 min. after therapy	140	16.1	8.42	
6	15	3.5-4.5	5-5.3	Control.....	145	13.25	5.76	Concentrated human
				3.5 hr.....	165	19.0	6.72	plasma, 110 cc. = 19.7
				4.5 hr.....	130	19.15	6.0	Gm. protein; lived
				32 min. after therapy	130	14.15	7.22	
7	8.8	3.3-3.75	4-4.3	Control.....	160	15.0	Concentrated human
				3.3 hr.....	175	19.65	plasma, 113 cc.;
				3.75 hr.....	160	20.15	lived
				1 hr. after therapy...	180	13.8	
8	10	4-4.5	4.75-5.3	Control.....	140	13.85	6.44	Concentrated human
				4 hr.....	155	22.0	6.72	plasma, 111 cc. = 21.2
				4.75 hr.....	130	21.65	6.44	Gm. protein; lived
				17 min. after therapy	142	15.0	7.04	
9	6.36	3.3-3.5	3.75-4.6	Control.....	148	14.15	5.6	Concentrated human
				3.3 hr.....	150	18.15	6.24	plasma, 86 cc. = 16.9
				3.75 hr.....	105	18.15	5.76	Gm. protein; lived
				38 min. after therapy	160	13.85	6.72	
10	10.45	3.5-3.9	4.3-4.9	Control.....	155	11.4	5.76	Concentrated human
				3.5 hr.....	130	plasma, 115 cc. = 21.1
				4.3 hr.....	135	18.65	6.48	Gm. protein; lived
				28 min. after therapy	145	10.9	6.4	
Aver.	10.0	3.3-3.99	4.3-4.86	Control.....	144.1	13.6	6.32	Concentrated human
				3.27 hr.....	151.3	19.7	6.78	serum and plasma,
				4.2 hr.....	125.3	19.4	6.47	96.2 cc. = 17.9 Gm.
				31.5 min. after therapy	141.1	14.2	6.96	protein; all lived

An average of thirty-one and five-tenths minutes after therapy with concentrated plasma (citrate) there was an increase in plasma protein concentration of only 0.49 Gm. per hundred cubic centimeters. This feature is once more taken to indicate a shift of fluid into the plasma stream. Again it was observed that the venous hemoglobin was usually not lowered to the control level in intervals up to thirty minutes after therapy.

HISTOPATHOLOGIC STUDIES

The appearance of various tissues in the late phases of this type of shock has been described.¹ The changes may be placed in three subdivisions: (1) vascular changes (mostly capillary and venous dilatation with packing of the red blood

cells); (2) interstitial changes (such as edema, capillary hemorrhages and leukocytic infiltration), and (3) parenchymatous changes (acute parenchymatous degeneration, fatty degeneration, atrophy, necrosis and necrobiosis involving mostly the liver, the kidneys and the adrenal cortex).

It seems noteworthy that the appearance of the tissues of the animals that died in group 1 (amputation; no protein therapy) and in group 2 (no amputation; protein therapy) was decidedly similar. The animals in group 1 that lived seven to fourteen days were included. In the latter group 1 animal (dog 10) had massive pulmonary edema with superimposed focal bronchopneumonia. All of these animals displayed capillariovenous stasis of the lungs, the myocardium, the

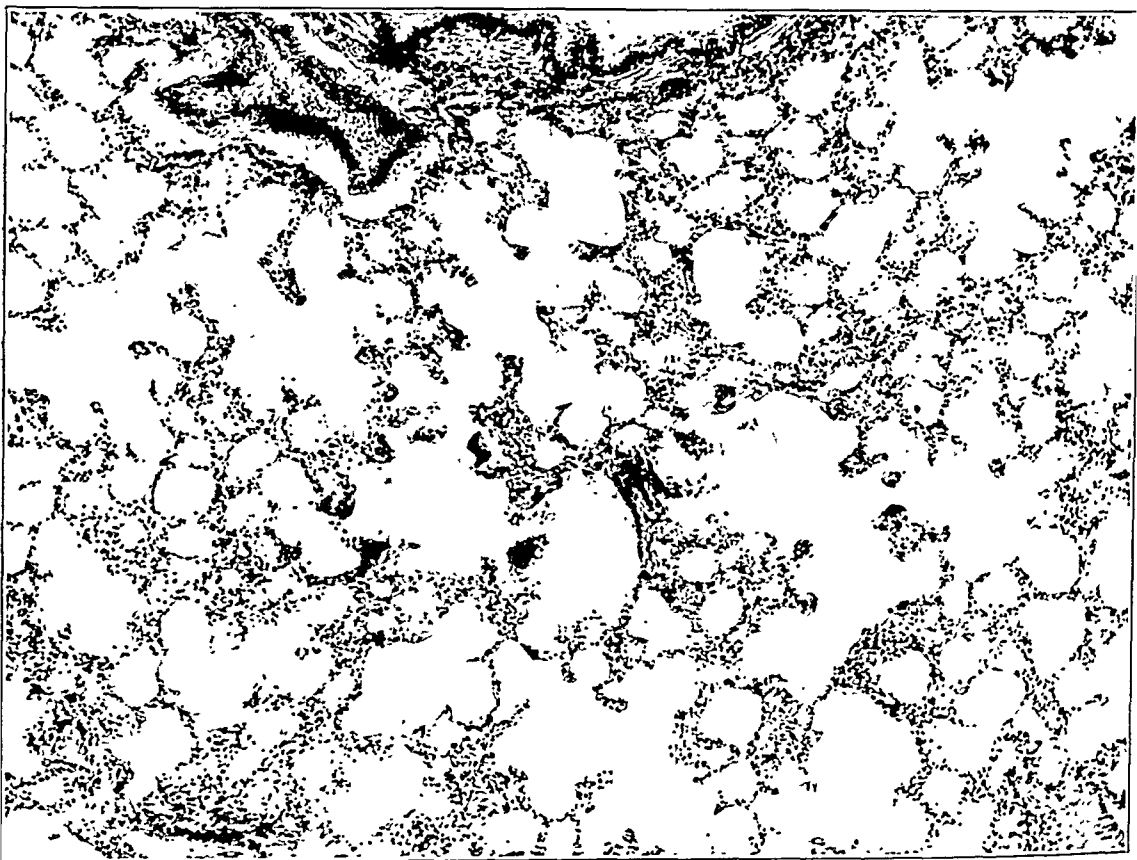


Fig. 1.—Dog 6, group 3 (amputation; protein therapy); lived; photomicrograph of a lung showing normal microscopic appearance. This animal was killed twenty-five days after the operation. See table 3 for other details.

liver, the kidneys and the adrenal cortex, pulmonary edema and small pulmonary hemorrhages, prominent atrophy of the hepatic cords (central) and the adrenal cortex, polymorphonuclear neutrophilic infiltration of the adrenal cortex and parenchymatous degeneration of the convoluted renal tubules. In addition, there was frequent central necrosis of the lobules of the liver and occasional focal necrosis of the renal tubules and the adrenal cortex. Precipitated protein material in the capsular space of the renal corpuscle and focal hyaline casts in the medullary tubules of the kidney were frequently observed. The spleen was firmly contracted and almost bloodless. Capillary dilatation of the intestinal mucosa was not as consistently observed as previously. Random samples of the somatic musculature

revealed only scattered dilated capillaries, and most of the muscle bundles had closely arranged fibers with collapsed intervening capillaries.

The parenchymatous lesions of the liver were more pronounced than in those observed in previous studies.¹ Two significant observations were made: First, the hepatic cords near the central vein were thin and narrow, so that the cells appeared elongated and the sinusoids widened. Second, there were frequent foci of coagulative necrosis, particularly near the central zones. In the latter areas the nuclear substance had disappeared. In 3 livers the necrosis involved over 50 per cent of the parenchyma in the sections examined, and there was confluence of several necrotic zones. Fatty degeneration was well advanced in 1 liver. The

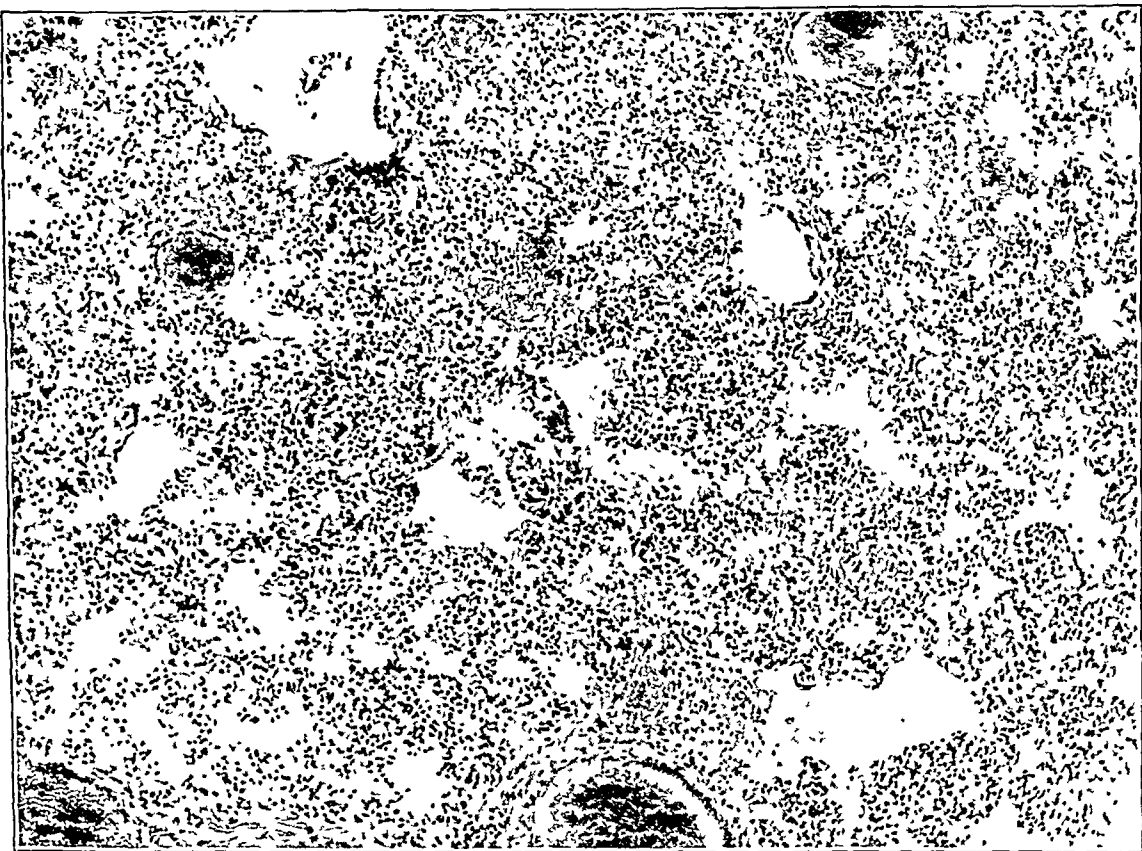


Fig. 2.—Dog 9, group 2 (protein therapy; no amputation); died in shock; photomicrograph of a lung showing pulmonary edema, capillariovenous congestion and capillary hemorrhages.

changes were more prominent in group 2 than in group 1. The dogs in the former group lived longer than those in the latter.

The hepatic lesions were similar to two types of lesions (central atrophy and central necrosis) described by Lambert and Allison¹⁰ in 1916 in relation to passive hyperemia of the liver associated with backward heart failure. Moon¹¹ has commented on the close similarity of the appearance of the viscera in shock and in generalized passive congestion, a feature borne out by these hepatic lesions.

10 Lambert, R. A., and Allison, B. R.: Types of Lesions in Chronic Passive Congestion of the Liver, *Bull. Johns Hopkins Hosp.* **27**:350-356 (Dec.) 1916.

11. Moon, V. H.: *Shock and Related Capillary Phenomena*, New York, Oxford University Press, 1938

The cells of the adrenal cortex (mainly zona fasciculata) in both group 1 and group 2 displayed a diffuse decrease in lipid content. There was loss of the normal foamy appearance, and the cytoplasm of the cells appeared narrow and dense and was partaking heavily of the eosin stain. Thus the cells of the zona fasciculata resembled the cells of the zona reticularis. Occasionally isolated areas of the zona fasciculata had cells that were indistinct and were seemingly undergoing a gradual necrosis or wasting away (necrobiosis). Patchy capillary hyperemia of the zona fasciculata and circumferential hyperemia of the zona reticularis were observed. As in previous studies, prominent infiltration of the cortex by neutrophilic leukocytes was frequently observed.

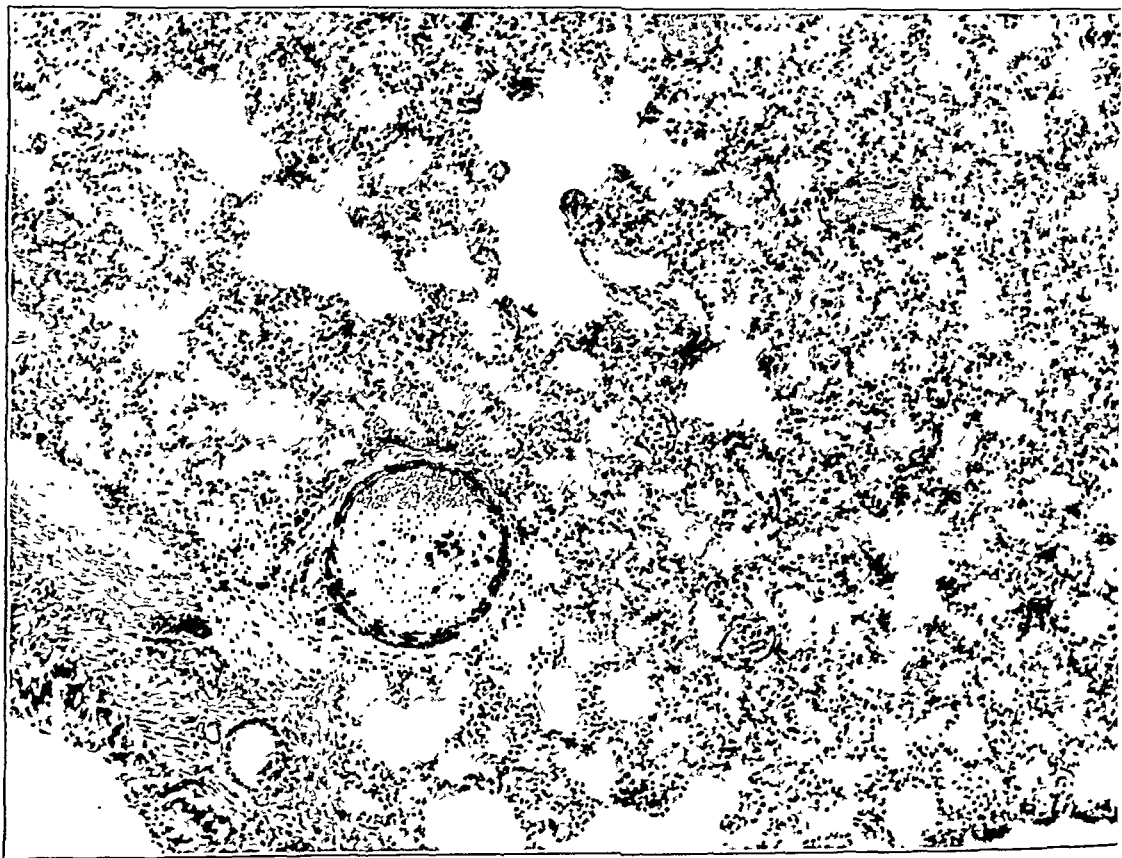


Fig. 3.—Dog 10, group 1 (amputation; no protein therapy); died ten days later; photomicrograph of a lung showing pulmonary edema, capillariovenous congestion and capillary hemorrhages.

Tissues from all of the animals in group 3 (amputation; protein therapy) were normal both grossly and microscopically. Tissues from dog 2 of group 1 were likewise normal. The livers of these animals had the usual lighter staining central areas and darker periphery observed in normal livers. The adrenal cortex was filled with lipid. There was no capillariovenous stasis, even in the region of the amputation. The scar of the amputation wound was dense in all cases and contained abundant collagen and well arranged fibroblasts. Focal areas of leukocytic infiltration were observed in these scars, but the inflammation present was chronic and localized. Healing was frequently complete by the time the animal was killed.

EFFECTS OF SODIUM CITRATE IN CONCENTRATED PLASMA

Sodium citrate binds ionic calcium rapidly, and for this reason it is commonly used as an anticoagulant. The excess sodium citrate in the plasma, above that bound to calcium, is capable of binding calcium in the blood stream. The binding effect on the calcium in the blood stream has been demonstrated¹² to be transient because the citrate is oxidized and the calcium liberated. Therefore, the organism after a sublethal intravenous injection of sodium citrate solution reverts rapidly to the preinjection state in so far as calcium ions are concerned. The citrate forms an alkaline ash which particularly tends to alkalinize excreta such as urine.

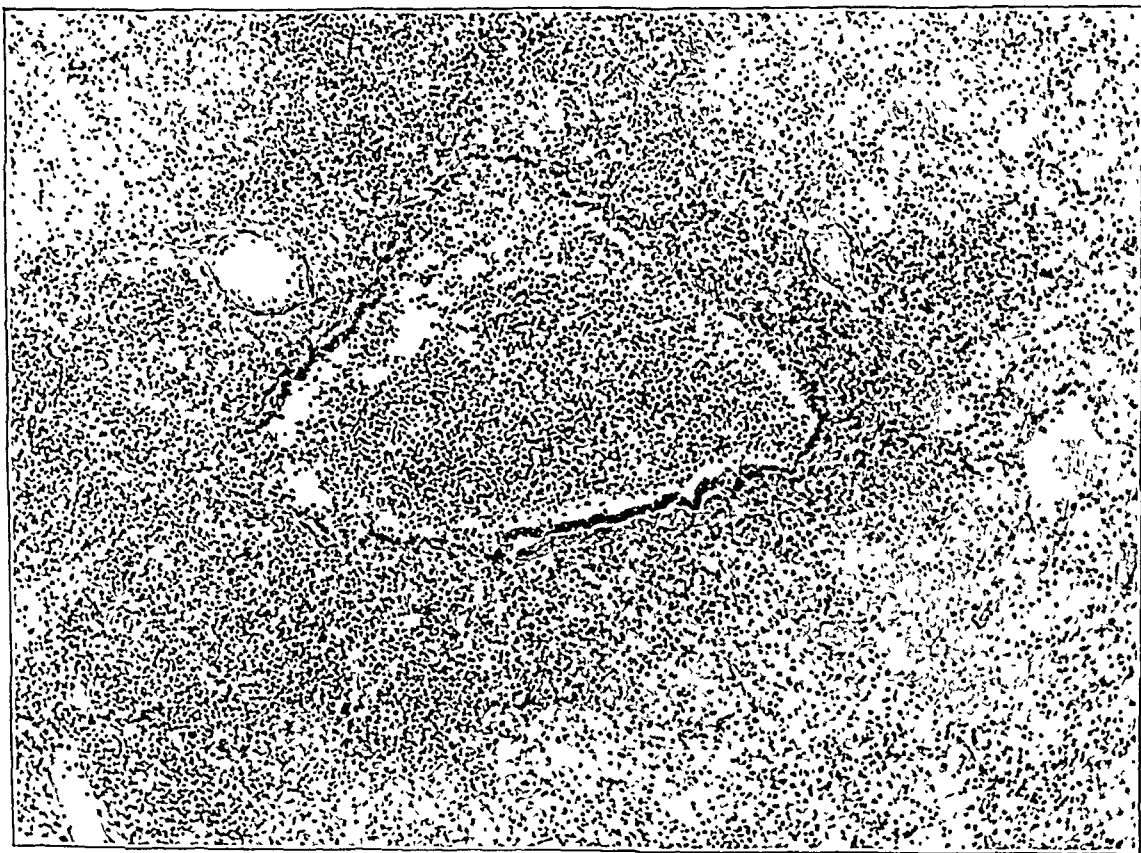


Fig. 4.—Dog 10, group 1 (amputation; no protein therapy); died ten days later; photomicrograph of the same lung as in figure 3, showing patch of bronchopneumonia superimposed on pulmonary edema.

The development of a calcium ion deficiency (manifested in the carpopedal spasm of tetany) after an intravenous dose of sodium citrate depends on the amount of citrate given per unit of time and on the calcium ion reserve of the recipient.¹³ The present indications are that the calcium reserve is not sufficiently

12. Salant, W., and Wise, L. E.: The Action of Sodium Citrate and Its Decomposition in the Body, *J. Biol. Chem.* **28**:27-58 (Dec.) 1916.

13. The state of the calcium ion reserve during shock, to our knowledge, has not been as completely studied as that of other ions, such as the potassium ion. G. W. Duncan's paper (Inorganic Phosphorus Content of the Serum in Shock, *Arch. Surg.* **46**:214-223 [Feb.] 1943)

depleted to constitute a complete contraindication to the use of citrated plasma in shock. This conclusion has been reached through a series of studies on the use of concentrated citrated plasma during shock in human beings and experimental animals, including the present studies. The solution must be used judiciously, particularly for small animals, in order to avert tetany and other more serious complications (such as cardiac standstill). Thus the amount of sodium citrate given per unit of time becomes the important factor. With dogs the doses of concentrated plasma must be given periodically, in order to allow for clearance of the blood stream of citrate and for accommodation of the circulatory system to the action of the concentrated solution.

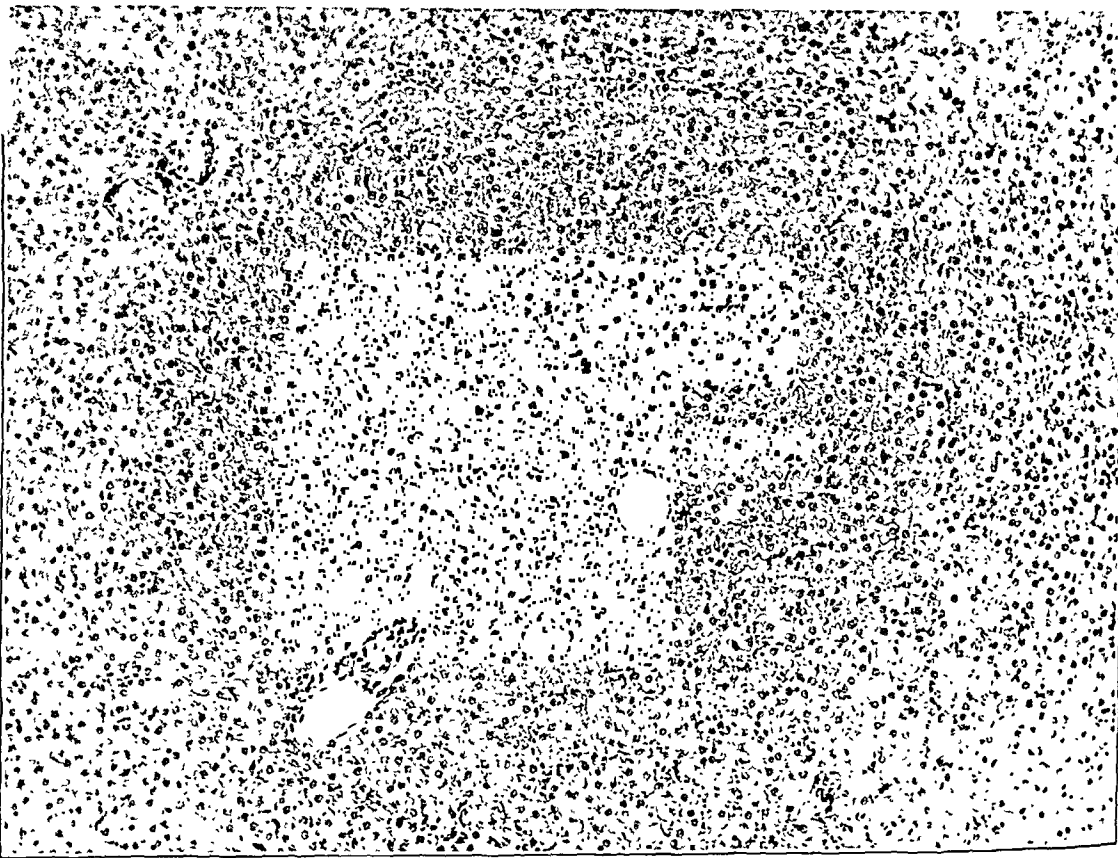


Fig. 5.—Dog 6, group 3 (amputation—protein therapy); lived; same dog as in figure 1; photomicrograph of the liver showing normal appearance, including darker and lighter zones. The width of the polygonal cells near the central vein is normal, and venosinusoidal hyperemia is absent.

In the present experiments 17 animals received concentrated citrated plasma. We were able to prevent or initiate tetany at will. Most of the 5 cc. doses (given in ten seconds) were spaced two to three minutes apart. Whenever 10 cc. doses

demonstrated conclusively an elevation of inorganic serum phosphate during shock and its development. The usual inverse relation to calcium at present appears unlikely, since the presence of a decrease in renal excretion should upset the usual reciprocal relation between these two substances. This view is supported by the observation of V. H. Moon (*The Vascular and Cellular Dynamics of Shock*, *Am. J. M. Sc.* 203:1-18 [Jan.] 1942) that in shock the blood calcium is increased.

were repeated every thirty to sixty seconds a severe spasm of tetany resulted sooner or later. The intravenous injection of 10 cc. of concentrated plasma in ten seconds constitutes too rapid an injection for dogs this size, for reasons to be mentioned hereinafter.

In several animals muscular tremors or fibrillations developed, involving the tongue and scattered muscles elsewhere. The fibrillations were probably based on a transient calcium deficiency, since they disappeared shortly after the therapy was concluded. This reaction, apparently a milder degree of tetany, occurred with some of the 5 cc. doses and signified that even some of these were spaced too closely together.

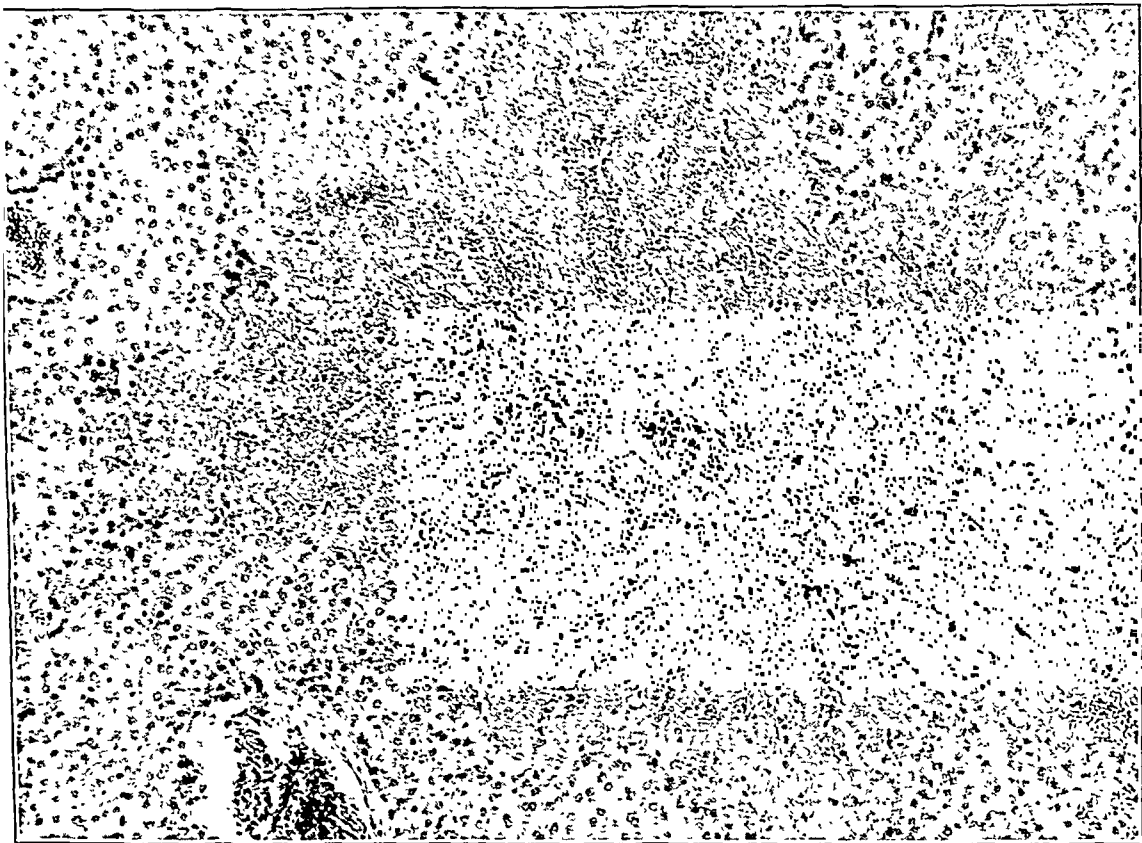


Fig. 6.—Dog 8, group 2 (protein therapy; no amputation); died in shock; photomicrograph of the liver showing coagulative necrosis of the central and midzonal portions of the lobule of the liver. One extension of this necrotic area became continuous with similar necrosis of an adjacent lobule. Over 50 per cent of the liver in this section of tissue was necrotic. The nuclear substance of the necrotic cells has disappeared.

Extreme caution must be exercised in interpreting the effects of citrate on dogs in terms of human beings. This care is necessary not just because one is dealing with two separate species. The dog is much lower in body weight; the vascular bed is smaller and the blood volume is much less. It is easy to inject 50 cc. of concentrated plasma into a dog weighing 10 Kg. in one minute, as we have done in the past.¹⁴ To administer a dose proportionate to the body weight of a

14. Muirhead, E. E.; Ashworth, C. T., and Hill, J. M.: The Therapy of Shock in Experimental Animals with Plasma Protein Solutions: I. Concentrated Plasma as a Hemodiluting Agent, *Surgery* 12:14-23 (July) 1942.

normal man weighing, let us say, 80 Kg., one would have to inject 400 cc. of concentrated plasma in one minute. We consider this rate very difficult to attain with ordinary syringes and needles, and although we have no experience with such rapid administration to human subjects, bad effects would be expected.

We have advocated the intravenous injection of 50 to 100 cc. of concentrated plasma to patients in shock in one to five minutes, with an interval of ten to twenty minutes between injections.¹⁵ In actual practice usually 100 cc. is given in five minutes.^{15c} If this rate is suitable for a human being weighing 80 Kg., a dog weighing 10 Kg. would require 2.5 cc. of concentrated plasma per minute for the period of actual administration, with intervening periods for circulatory accom-

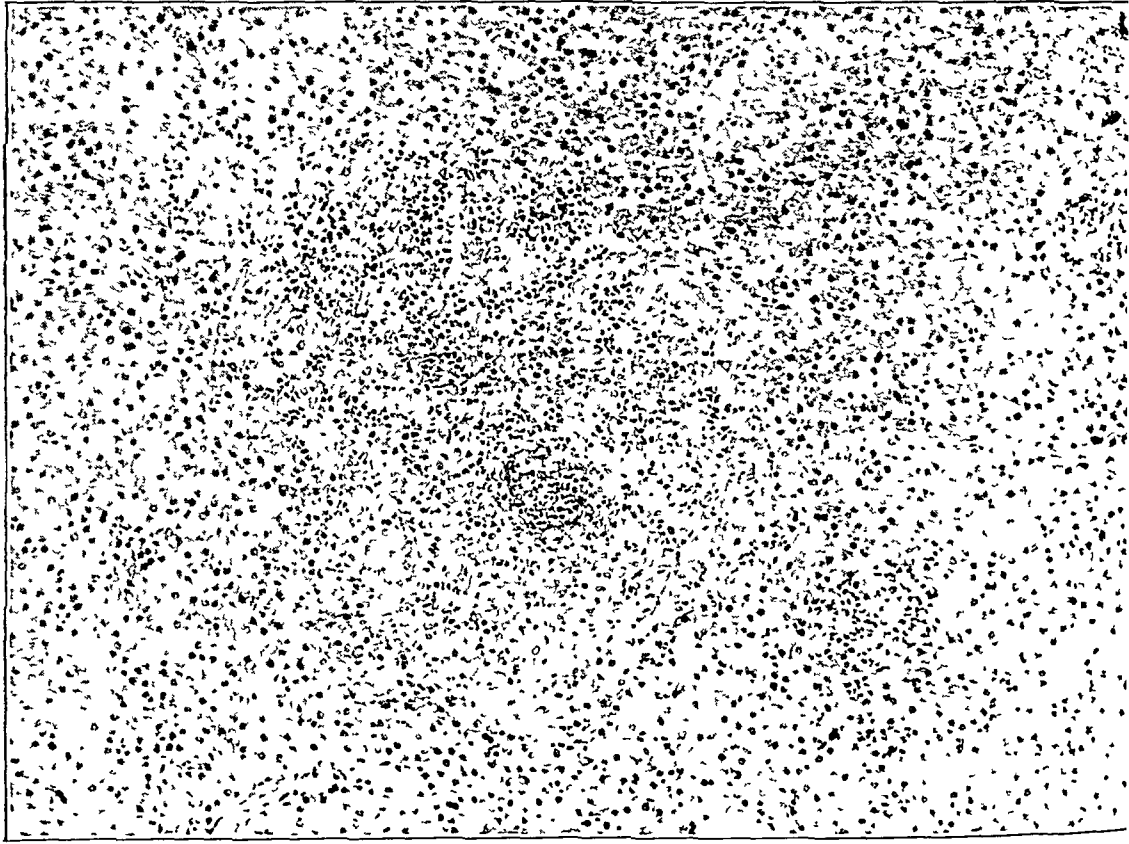


Fig. 7—Dog 3, group 1 (amputation; no protein therapy); died in shock; photomicrograph of the liver showing central necrosis and moderate fatty degeneration of viable liver cells. There is slight infiltration of the necrotic area by polymorphonuclear neutrophilic leukocytes. Once more there is a notable absence of nuclear remnants in the necrotic liver cells.

modation. The average rate of injection in the present experiments was 5 to 10 cc. in ten to thirty seconds. This rate, which was far beyond the human rate, admittedly exceeded the limits we had set and will be discussed under the depressor effect.

15. (a) Hill, J. M.; Muirhead, E. E.; Ashworth, C. T., and Tigertt, W. D.: The Use of Desiccated Plasma with Particular Reference to Shock, *J. A. M. A.* **116**:395-402 (Feb. 1) 1941. (b) Hill, J. M., and Muirhead, E. E.: The Use of Desiccated Plasma in Urology, *J. Urol.* **47**:387-394 (March) 1942. (c) Muirhead, E. E.; Ashworth, C. T., and Hill, J. M.: The Use of Human Plasma Protein Solutions in Surgery, *South Surgeon* **11**:413-431 (June) 1942.

In conclusion, tetany resulted in the present experiments only when the injections were spaced too closely together. It appears, then, from practical experience that the judicious use of concentrated plasma for shock in small animals or in human beings need not be accompanied by tetany or other acute effects of sodium citrate on the circulation.

TRANSIENT DEPRESSOR EFFECT

Concentrated serum containing 15 Gm. per hundred cubic centimeters of protein has been observed by us³ to produce a transient depression of the mean arterial pressure in dogs when doses of 5 to 20 cc. are given intravenously in five

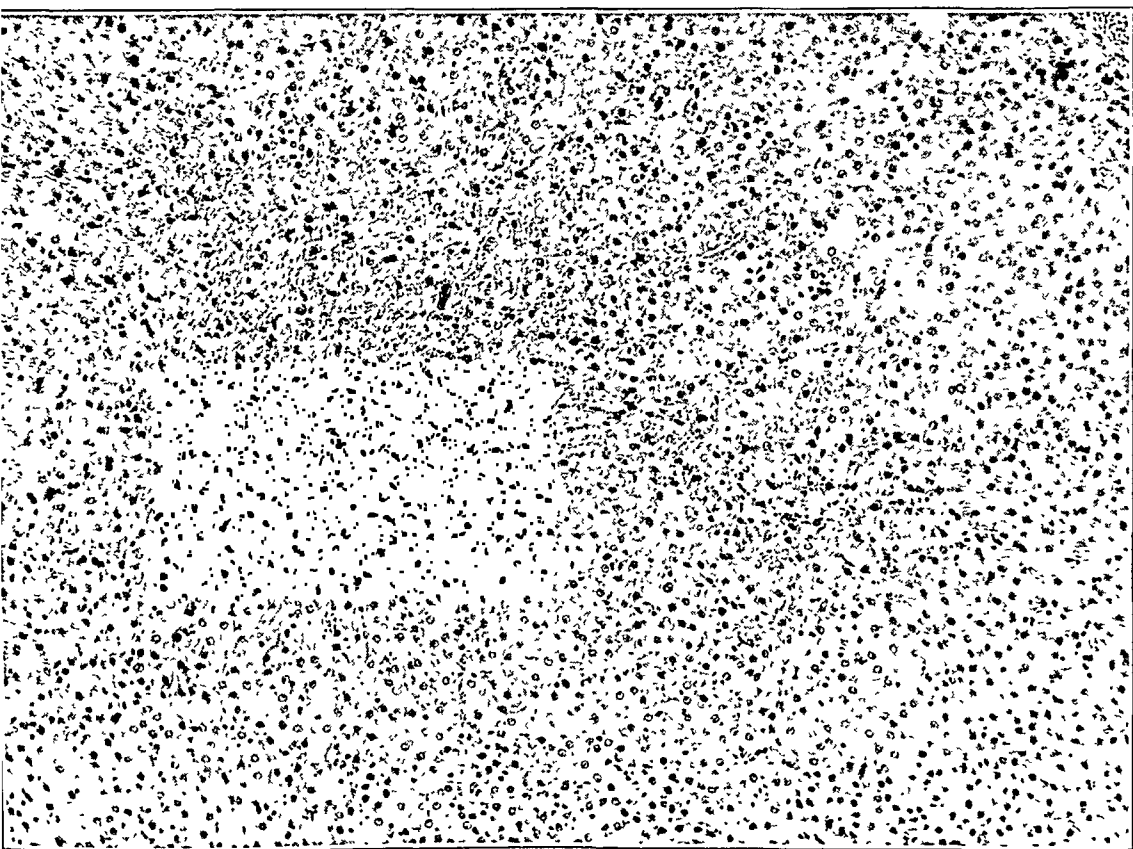


Fig. 8.—Dog 4, group 2 (protein therapy; no amputation); died in shock; photomicrograph of the liver showing atrophy of the cord cells in the central portion of the lobule. The sinusoids appear considerably widened. Compare these cells with those in figure 5.

to thirty seconds. This effect varied somewhat from animal to animal but could be elicited consistently when larger doses (15 to 20 cc.) were given rapidly (ten seconds). These observations were substantiated in the present experiments with both concentrated plasma and serum given to animals with normal, slightly elevated or slightly depressed arterial pressures.

The depressor effect consisted of a transient drop in mean arterial pressure followed by complete recovery. With subjects whose arterial pressure was depressed, recovery was associated with a rise in pressure above the initial level. The entire effect lasted thirty to sixty seconds. When larger doses were given, the pressure was lowered by 15 to 25 mm. of mercury. Occasionally in instances

when the original pressure was high (190 to 200 mm. of mercury) the decrease amounted to as much as 40 mm. of mercury. Hyperpnea at times accompanied the effect.

In this connection a technical point related to the sodium citrate solution used in the mercury manometer setup should be remembered. When the arterial pressure drops, citrate solution is forced into the carotid artery and when the drop is considerable, enough sodium citrate may dam back into the heart to precipitate a citrate effect and exaggerate the effect due to sodium citrate in the plasma. To avoid this complication we have used a heparin solution in other experiments.

This depressor effect has been studied further, and the results form the basis for a separate report.¹⁶ For the present we should like to point out that a similar

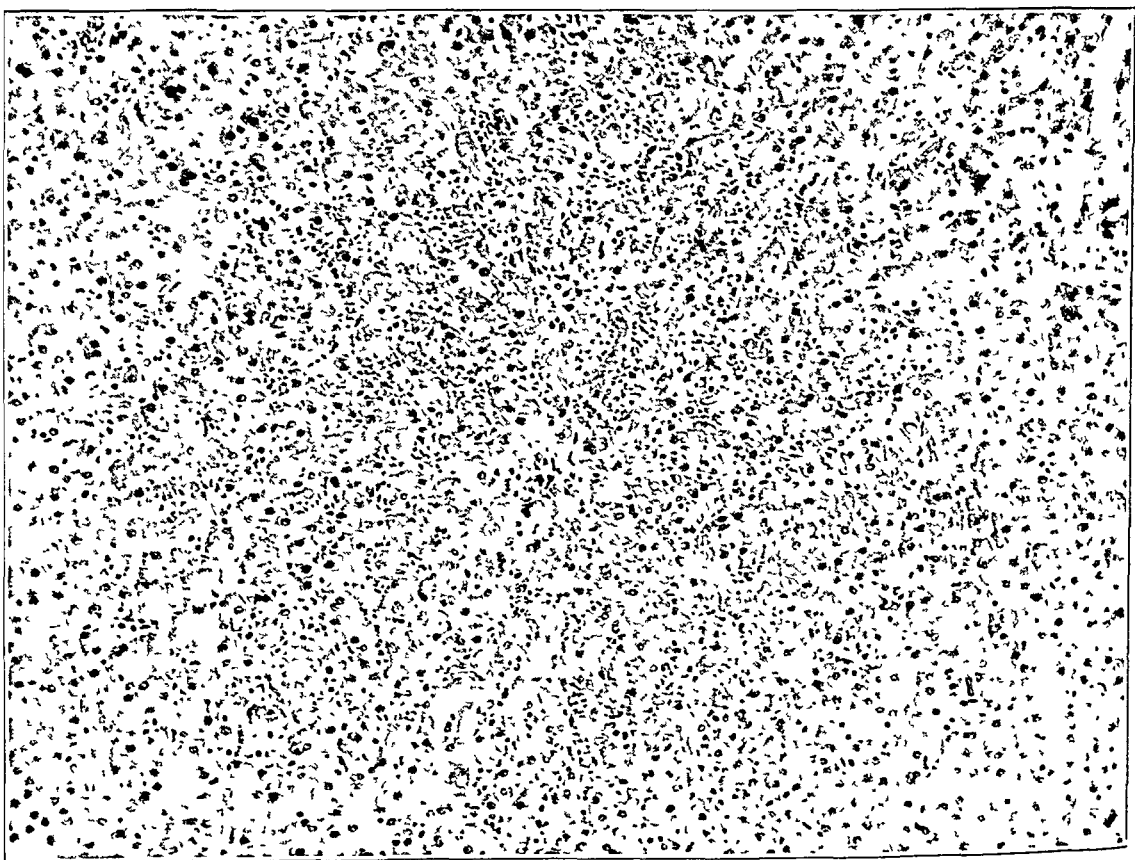


Fig. 9.—Dog 7, group 1 (amputation; no protein therapy); died in shock; photomicrograph of the liver showing central atrophy of the hepatic cells. As the hepatic cords approach the region of the central vein they become thin and narrow, so that frequently the nuclei are adjacent to the limiting cell membrane. There are focal areas of fatty degeneration.

depressor effect can be elicited in normal dogs or dogs suffering from freezing shock or hypotension due to hemorrhage by the rapid injection of any of the following solutions: concentrated plasma and serum, 50 per cent solution of dextrose, 10 per cent solution of sodium chloride, 3 per cent solution of sodium chloride and 20 per cent solution of acacia. In our experience, isotonic solutions

16. Muirhead, E. E.; Lacke, R.; Bunde, C. A., and Hill, J. M.: The Depressor Effect Following the Very Rapid Intravenous Injection of Concentrated (Hypertonic) Solutions to Dogs, unpublished data.

in the same volume and rate have not precipitated a similar effect. Isotonic solutions given in larger, comparable volumes elicit a different depressor response.

The concentrated solution must reach the cardiac-pulmonary region rapidly in order to effect a response. The injection of 10 to 15 cc. in forty-five to ninety seconds instead of five to fifteen seconds has consistently failed to produce this response.

It appears, therefore, that the speed of injection and the concentration of the solutes are the main factors producing this response. In the present experiments most of the injections were given sufficiently rapidly to initiate the transient depression, but any single injection that was given at a relatively slower rate



Fig. 10—Dog 6, group 3 (amputation; protein therapy); lived; photomicrograph of an adrenal gland showing capsule, zona glomerulosa and zona fasciculata. The appearance is normal, with cells well filled with lipid, which gives them a foamy appearance

failed to produce it. According to our criteria, however, the end results of the injections in each instance appeared to be beneficial to the circulation.

In this connection, as was the case with the citrate reactions, it would seem that caution is needed in interpreting the results in terms of human beings. If the previous basis for comparison is used, it appears that doses as high as 300 to 600 cc. of concentrated plasma given in one minute to human adults weighing 80 Kg. would be required to effect similar changes. Therefore, the margin of safety in man appears great, but care seems necessary in studying the treatment of experimental shock in animals with concentrated plasma and serum, since it is

easy to overtax the animals' ability to handle the solutions. Intermittent injections of 2.5 to 15 cc. given in forty-five to one hundred and twenty seconds seem to be adequate.

GENERAL COMMENT

Severe freezing of one hind extremity of a dog produces widespread damage to capillaries and tissues after thawing. In the 2 dogs which survived for a few days the extent of the injury was emphasized by the fact that the limb became completely gangrenous. This injury leads to a series of events culminating in severe oligemia and cellular damage to the viscera. Previous study³ indicated that



Fig. 11.—Dog 1, group 2 (protein therapy; no amputation); died in shock; photomicrograph of an adrenal gland showing the capsule, zona glomerulosa and zona fasciculata. There is a considerable difference from figure 10. The cells of the zona fasciculata are narrow and dense and display a marked decrease in lipid content. There are scattered polymorphonuclear neutrophilic leukocytes.

visceral damage became evident beyond the fourth hour. The present experiments indicate that removal of the limb between the third and the fourth hour is not in itself sufficient to assure recovery (group 1). Only 2 animals in this group marshaled recovery mechanisms adequate to cope with damages wrought by the shocking procedure plus operation. In the majority (8 of 10) the pathogenesis of shock continued unhampered, or at the most they lingered a few days only to die of complications related to the shocking procedure. The results obtained with group 2 seem to indicate that a single replacement of the plasma volume and

circulating proteins during the apparent borderline period of advanced visceral damage likewise fails to bring about life-saving recovery if further therapeutic measures are not taken. A combination of removal of the damaged site plus immediate plasma volume and protein replacement (group 3) was successful in preventing the further advancement of the pathogenesis of shock and allowed for complete recovery. In group 3, moreover, the demonstrated lack of active or residual cellular damage and the absence of evidence of previous cellular damage with repair of the viscera indicated that the prevention of fatal shock occurred before pathologic changes were sufficiently pronounced or advanced to overwhelm the organism.



Fig 12—Dog 3, group 1 (amputation, no protein therapy), died in shock, photomicrograph of an adrenal gland showing the capsule, zona glomerulosa and zona fasciculata. There is a decrease in the lipid content, which is not as marked as in figure 11, and scattered leukocytes are seen.

The present experiments seem to afford no new evidence to settle the controversy between those who hold that shock is due to toxemia¹⁷ and those who maintain that it is due to local loss of fluid from the plasma.¹⁸ The visceral lesions in the dogs of group 1 and group 2 were similar, that is, no deviation in the type of lesion resulted from the removal of the damaged limb before the apparent

17. Moon, V. H. *Shock: Its Dynamics, Occurrence and Management*, Philadelphia, Lea & Febiger, 1942.

18. Blalock, A. *Principles of Surgical Care: Shock and Other Problems*. St. Louis, C. V. Mosby Company, 1940.

borderline period of advanced visceral damage. It seems true that the lesions were similar to the type encountered whenever there is stagnation of the circulation, as those who have examined autopsy material from patients who had passed through a period of failure of the right side of the heart would verify, or a decrease in transport of oxygen to the tissues. Thus the hepatic lesions resembled the lesions of passive hyperemia described by Lambert and Allison,¹⁹ the lesions of severe anemia described by Rich¹⁹ and certain lesions due to experimentally induced anoxia.²⁰ On the other hand, certain toxic agents conveyed by the blood stream are known to produce central necrosis of the liver.²¹ Moon¹¹ has emphasized the similarity in the appearance of the visceral lesions due to generalized passive



Fig. 13.—Dog 3, group 1 (amputation; no protein therapy); died in shock; photomicrograph of a kidney showing hyaline casts in the medullary tubules. Granular protein material was observed in the capsular spaces of Bowman's capsule.

hyperemia, asphyxia and shock. The only evidence that a sustained hypoxemia resulting from the oligemia was solely responsible for the visceral lesions encountered in the present experiments is the similarity between these lesions and those resulting from an induced simple anoxia. One cannot question the concept

19. Rich, A. R.: The Pathogenesis of the Forms of Jaundice, *Bull. Johns Hopkins Hosp.* **47**:338-377 (Dec.) 1930.

20. McIver, M. A., and Winter, E. A. Deleterious Effects of Anoxia on the Liver of the Hyperthyroid Animal, *Arch Surg* **46**:171-185 (Feb.) 1943.

21. MacCallum, W. G.: *A Text-Book of Pathology*, ed 6, Philadelphia, W. B. Saunders Company, 1936, p. 298

that absorbed toxic agents are responsible for the parenchymatous damage and pulmonary edema (the toxic theory) on such meager collateral evidence. Nevertheless, one could not but be impressed with the amount of fluid in the damaged limb during these experiments, whether treatment was given or not. The limbs of the dogs in group 2 were huge. Seven specimens of the abundant subcutaneous fluid at the site of damage when analyzed yielded an average protein concentration of 4.7 Gm. per hundred cubic centimeters. This fluid was free from red cells and approached the circulating plasma in protein content. Therefore, the escape of protein-containing fluid into the damaged limb appeared to play a prominent role in the pathogenesis of fatal shock of dogs in groups 1 and 2.

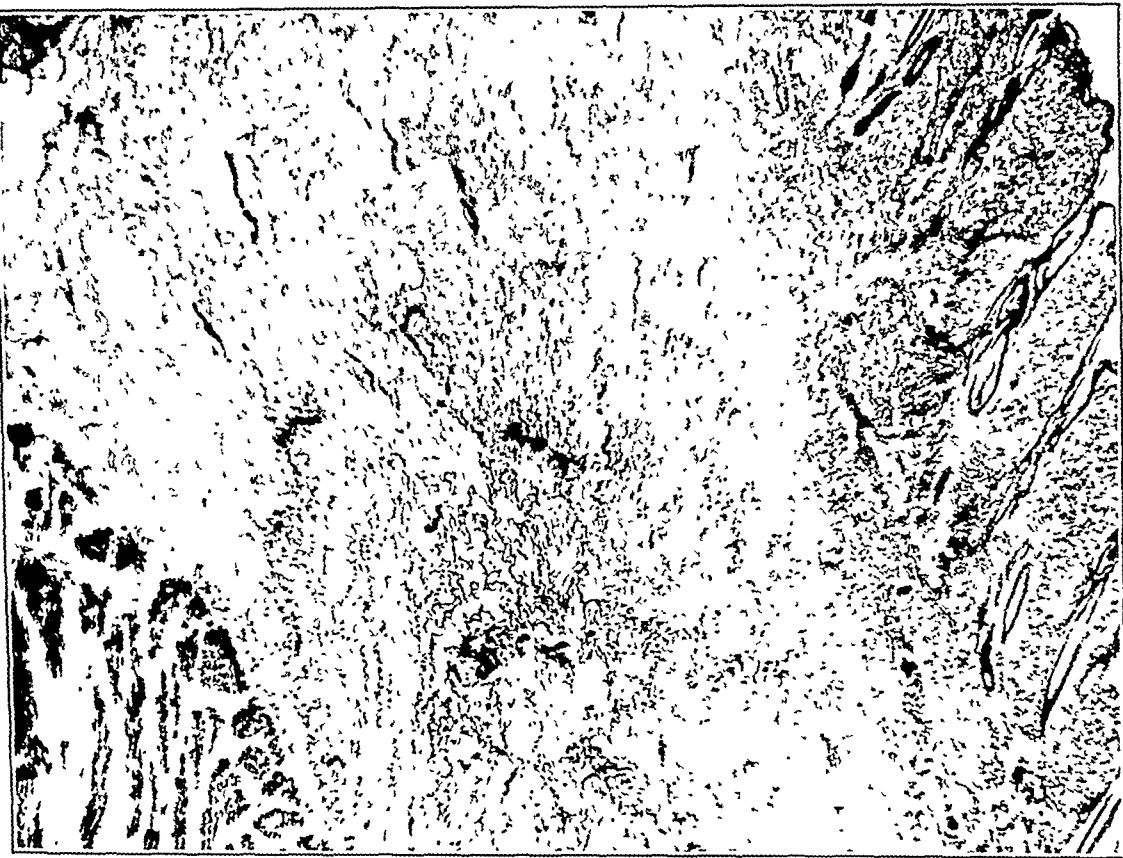


Fig. 14.—Dog 2, group 3 (amputation; protein therapy); lived; photomicrograph of skin and subcutaneous tissue of the frozen-thawed site (amputated limb) showing edema of the subcutaneous tissues. The connective tissue fibers are separated by a granular, pink precipitate similar to that observed in the alveoli of the lungs in pulmonary edema. This precipitate represents a protein-containing fluid.

The work of Sir Thomas Lewis²² has demonstrated the presence of substances at the site subjected to freezing and thawing capable of dilating the capillaries and increasing their permeability to plasma colloids and has made it clear that this is a mechanism likely to be involved in the process of local fluid loss. Previous studies¹ indicated that the loss of fluid at the site of freezing and thawing appeared to be predominant before generalized capillary atony and pulmonary edema

22. Lewis, T., and Love, W. S. Vascular Reactions of Skin to Injury: III. Some Effects of Freezing, of Cooling and of Warming, *Heart* 13:27-60 (Aug) 1926.

appeared. Of course, it was not established whether the absorption of the harmful agents from the damaged site was responsible for the ultimate generalized visceral damage or whether hypoxemia was solely causative. In this connection, therefore, one agrees with the compromise offered by Solandt and Best²³ and based on their study of other types of shock-producing injuries. They stated that in shock due to freezing local loss of fluid is a major etiologic factor, but that "almost certainly other unknown factors are operative."²³

The controversies regarding the pathogenesis of shock are once more alluded to in order to emphasize the difficulties involved in explaining the results of the present experiments.



Fig. 15.—Dog 2, group 3 (amputation; protein therapy); lived; photomicrograph of the healing amputation site ten days after the operation. There are many fibroblasts in parallel arrangement, with abundant intercellular material. The skeletal muscle is normal in appearance. Same dog as in figure 14.

The proponents of the toxic theory would explain the results by claiming that in group 3 when the toxin-bearing area had been removed the improvement of the circulation by intravenous protein therapy allowed for recovery from the early damage due to the absorbed toxins, that in group 2 the toxin-bearing area continued to contribute harmful agents leading to fatal shock (also an explanation

23. Solandt, D. Y., and Best, C. H.: Studies on the Etiology of Traumatic Shock, in Mudd, S., and Thalhimer, W.: Blood Substitutes and Blood Transfusion, Springfield, Ill., Charles C Thomas, Publisher, 1942.

for the greater severity of hepatic lesions) and that in group 1, without an improved circulation, the organism was unable to cope with the early damage by toxins and the superimposed hypoxemia. Those who uphold the theory of local loss of fluid would claim that in group 3 the removal of the damaged extremity did away with the site of plasma loss and that with therapy the circulation was reestablished and maintained before the onset of irreversible failure, so that recovery ensued; that in group 2 the site of local fluid loss was maintained and oligemia and fatal shock were produced, and that in group 1 the lowered circulating volume following amputation was sufficient to allow hypoxemia to produce the generalized changes.

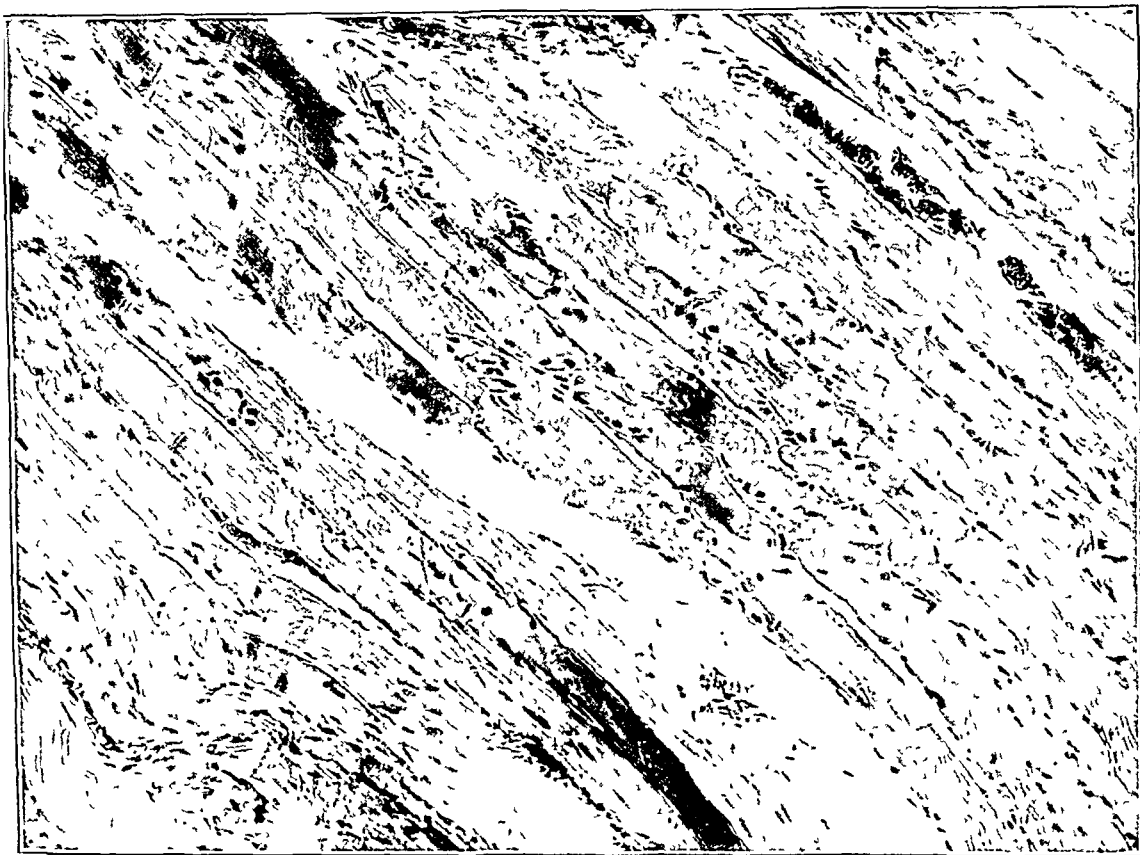


Fig. 16.—Dog 2, group 2 (protein therapy; no amputation); died in shock; photomicrograph of somatic musculature remote from the frozen-thawed site. There are several venules stuffed with red blood cells and an occasional open capillary. There is no edema; the muscle fibers are normal in appearance, and most of the capillaries are closed.

With regard to other controversial features in the field of shock therapy, we feel more certain of several deductions. There should be no doubt that concentrated plasma and serum, properly prepared and administered, are capable of improving the circulation during shock by increasing the plasma volume and circulating proteins. By all present indications, the action occurs at capillary sites where fluid is withdrawn into the circulation. A previous study² indicated that the venous hemoglobin is not an accurate guide to the degree of increase in plasma volume, since greater numbers of red cells seemed to be released into the general

circulation from capillary sites. Such an event would explain the fact that in the present experiments the venous hemoglobin concentration failed to return to the control level, even in group 3, despite a minor degree of loss of blood during the operation. The absent or slight elevation of the recipient's plasma protein concentration in the presence of intravenous injections of a concentrated protein solution is indicative of the passage of fluid into the plasma stream.

The observations presented in this paper and in others²⁴ are in disagreement with the observations of Mahoney, Kingsley and Howland.²⁵ These investigators observed essentially no beneficial effects on the circulation after the intravenous administration of concentrated plasma to dogs in a state of shock resulting from intestinal trauma and reasoned that in the presence of the circulatory failure of shock concentrated plasma is unable to draw fluids back into the circulation. The solutions were not injected intermittently but given continuously by vein. The plasma protein concentration of the recipient was elevated, and it was stated that in certain of the animals receiving 200 cc. of concentrated plasma as a prophylactic dose (begun at the same time as trauma), "the plasma volume would remain essentially unchanged during the injection, but in spite of this the blood pressure fell, followed by death of the animal." It was not stated whether the plasma was prepared with sodium citrate, and the protein concentration of the material given and the specific weights of the animals given the solutions were not reported. It would seem that variations between the amounts of protein and the technics of administration used by us and those used by Mahoney, Kingsley and Howland and us have had a great deal of influence on the differences in results.

The therapeutic doses used by Mahoney, Kingsley and Howland were 45 to 50 cc. of concentrated plasma and as much as 700 cc. of dilute plasma for animals weighing "from 15 to 25 Kg." Usually 30 cc. of four times concentrated plasma contains between 10 and 12 Gm. of proteins. The 700 cc. of dilute serum, with a protein concentration of 3 to 4 Gm. per hundred cubic centimeters, contained between 21 and 28 Gm. of protein. Inasmuch as certain animals exhibited a deficit of as much as 37 Gm. of circulating proteins during shock, one can appreciate the gross differences in the replacement of lost circulating proteins by these two volumes of solutions and consequently the grossly different effects on the circulation.

If one assumes that the plasma solutions were prepared with sodium citrate, one can appreciate why a fatal termination occurred for certain animals without changes in the plasma volume. Ivy and his associates²⁶ observed that a single replacement infusion of citrated plasma after a copious hemorrhage was not as efficient as one of heparinized plasma and reasoned that the effects of the citrate were responsible for the difference. Since a greater amount of calcium is bound per unit of time by the injection of concentrated or of normal plasma than by the injection of dilute plasma, the severity of the effects would necessarily be greater with the former two solutions. On previous occasions¹⁴ we observed death of animals who had been subjected to exceedingly rapid administration of concentrated citrated plasma.

24. Muirhead, Ashworth, Kregel and Hill.³ Muirhead, Ashworth and Hill, footnotes 14 and 15c.

25. Mahoney, E. B.; Kingsley, H. D., and Howland, J. W.: *The Treatment of Experimental Shock by the Intravenous Injection of Dilute, Normal and Concentrated Plasma*, Surg., Gynec. & Obst. **74**:319-325 (Feb., no. 2 A) 1942.

26. Ivy, A. C.; Greengard, H.; Stein, I. F., Jr.; Grodins, F. S., and Dutton, D. F.: *The Effect of Various Blood Substitutes in Resuscitation After an Otherwise Fatal Hemorrhage*, Surg., Gynec. & Obst. **76**:85-90 (Jan.) 1943.

The recent observations of Levinson, Weston, Janota and Necheles²⁷ that the arterial pressure is depressed temporarily after injections of concentrated serum are apparently of the same nature as those discussed under the heading of transient depressor effect, since Levinson, Weston, Janota and Necheles injected 50 cc. of the concentrate in one minute into dogs in hemorrhagic shock. In an earlier report¹⁴ we observed harmful effects from a similar rate of injection of concentrated plasma but attributed most of the results to the sodium citrate in the solutions. It appears evident now that at least part of the ill effects resulted from the too rapid administration of the concentrated solutions.

SUMMARY AND CONCLUSIONS

Severe freezing of one hindlimb, an injury previously determined to produce fatal shock in dogs within an average of eight hours, was produced, and the following three therapeutic procedures were instituted for groups of 10 dogs each: In group 1, the damaged extremity was amputated between three and two-tenths hours and three and nine-tenths hours (average) after the freeze was terminated and the effects observed; in group 2, intravenous injections of concentrated plasma, in amounts previously determined to effect a sufficient replacement of the plasma volume was instituted between four and two-tenths and four and nine-tenths hours and the effects observed; in group 3, the damaged limb was amputated between three and three-tenths and three and ninety-nine hundredths hours (average) after the freeze was terminated and adequate intravenous injections of concentrated plasma were instituted between four and three-tenths and four and eight-tenths hours (average). Previous study had revealed that advanced visceral damage appeared after the fourth hour.

The following results were obtained: in group 1, 8 of 10 dogs died after a few hours in shock or after a few days of complications resembling the shock picture; in group 2, all 10 dogs died in shock, 8 of them within a relatively few hours; in group 3, all dogs lived and appeared healthy subsequently.

Concentrated plasma increased the circulating plasma volume and circulating plasma proteins by withdrawing fluids into the plasma stream. This effect was demonstrated by a meager or no elevation of the recipient's plasma protein concentration.

As has been previously observed, the degree of venous hemodilution following the administration of concentrated plasma was not complete, although one would expect it to be so after an adequate replacement of plasma volume. This phenomenon seemed to indicate the presence of greater numbers of red blood cells, possibly released from capillary sites, in the general circulation.

Histopathologic studies revealed that the visceral lesions of groups 1 and 2 were similar. The hepatic necrosis was unique in that we had not observed such severe damage in this type of shock before, possibly because the animals lived longer than those used for previous studies. The damage to the viscera of the dogs in groups 1 and 2 demonstrated what was prevented in group 3. The viscera of the dogs in the latter group were normal and revealed no residual damage or evidence of damage with repair. Apparently the prevention of visceral damage was complete.

Emphasis has been placed on the effects of sodium citrate in binding the calcium in the plasma, because differences of opinion appear to have resulted from this

27. Levinson, S. O.; Weston, R. E.; Janota, M., and Necheles, H.: Effects of Concentrated Serum in Contrast to Iso-Osmotic Plasma on Normal and Dehydrated Dogs in Shock, *Surgery* 12:878 (Dec.) 1942.

property. It has been stressed that concentrated plasma should be injected by vein in intermittent doses for two reasons: (1) to allow for oxidation of the citrate and (2) to allow for accommodation of the organism to the concentrated solutions.

The transient depressor effect of concentrated solutions when they are injected very rapidly by vein into small animals (dogs) has been discussed. The difference in response of small animals and adult human beings has been pointed out.

The results have been discussed with reference to two leading theories of the pathogenesis of shock, that of toxemia and that of local loss of plasma. The absorption of harmful agents from the damaged site could not be questioned on the basis of the results obtained, but local loss of fluid appeared to be a prominent etiologic factor.

Mr. Kenneth Stemmler, a fourth year student in the medical school, assisted in these experiments as his senior year problem. The photomicrographs were prepared by Mr. Lewis Waters of the Medical Arts Department. Miss Mary Seamen prepared the tissue sections. Miss Inagene Blair determined the protein concentrations.

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FROZEN SHOULDER; PERIARTHRITIS; BICIPITAL TENOSYNOVITIS

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Of the various conditions known to affect the periphery of the shoulder joint, least is known about periarthritis, or frozen shoulder. Although the illness was clinically identified many years ago, it continues to be known by an inaccurate name, its pathology remains mysterious and views regarding its therapy are divergent and confusing. The present study is concerned with evidence in support of the contention that the basic lesion in so-called periarthritis or frozen shoulder is bicipital tenosynovitis. Correlation of the clinical and pathologic observations to be herewith reported clarifies the mechanism which underlies the illness, explains its remarkable spontaneous cure and furnishes a sound basis on which conservative and surgical therapy may be planned.

CHRONOLOGY

The contributions of Duplay¹ at the close of the nineteenth century represent the first effort to distinguish "humeroscapular periarthritis" from the vague general classification "arthritis." The disease that Duplay described corresponds clinically to what now is termed "frozen shoulder," and he attributed it to subacromial bursitis. By the name "periarthritis" Duplay meant something more than a lesion peripheral to the shoulder joint proper. He regarded the subacromial bursa as an accessory shoulder joint, or periarthros, and to Duplay periarthritis meant specifically an inflammation of this structure. Duplay recommended manipulation with the patient under anesthesia for alleviation of the stiffness. These papers were published prior to and coincident with the invention of the roentgen ray apparatus, so that the author was unable to recognize and distinguish those shoulders with calcific deposits. In the decade following, the use of roentgen examinations became widespread. Calcified deposits in painful as well as in asymptomatic shoulders were encountered, and in 1907 Baer² and Painter³ published the first papers in this country advocating removal of the deposits for relief of pain. The greater part of the medical profession, however, was slow to accept the existence of any clinical distinction between painful shoulders with calcific deposits and those without them. The term "periarthritis" continued to be employed to describe many varieties of abnormal conditions of the shoulder, and subsequent literature is rich in controversial papers on the subject. Pleas for a pathologic interpretation of pain in the shoulder were frequently expressed (King and Holmes⁴), but as late as 1931

1. Duplay, S.: *De la périarthrite scapulo-humérale*, Rev. prat. d. trav. de méd. **53**:226, 1896; translated, M. Week **4**:253, 1896; *On Scapulo-Humeral Periarthritis*, M. Press **59**:571-573, 1900 Duplay wrote a monograph on scapulohumeral periarthritis in 1872, but I have been unable to locate this early paper.

2. Baer, W. S.: *Operative Treatment of Subdeltoid Bursitis*, Bull. Johns Hopkins Hosp **18**:282-284, 1907.

3. Painter, C. F.: *Subdeltoid Bursitis*, Boston M. & S. J. **156**:345-349, 1907

4. King, J. M., Jr., and Holmes, G. W.: *Diagnosis and Treatment of Four Hundred and Fifty Painful Shoulders*, J. A. M. A **89**:1956-1961 (Dec. 3) 1927

Mumford and Martin⁵ and in 1932 Dickson and Crosby⁶ published comprehensive papers on the subject and stated that they could observe no *clinical* difference between the two groups of cases. Although Mumford and Martin wrote, "In none of the very severe 'painful' shoulders in which there is a marked loss of function due to firm adhesions . . . did a deposit occur," this correct observation was incorrectly taken by the authors to indicate that the calcium deposits noted on roentgen examination are of no importance. Sporadic publications still appear⁷ which indicate no appreciation of the clinical difference between the two groups of cases.

The comprehensive studies of Codman⁸ served a threefold purpose in clarifying the situation. In the first place, Codman settled beyond further doubt that cases of pain in the shoulder associated with calcific deposits constitute a separate entity. Following his lead, those of us who have observed the rapid disappearance of symptoms after surgical removal of the deposits can no longer doubt their causal relationship to the pain. Secondly, Codman identified the ruptures of the supraspinatus tendon and so removed another large group of cases from the heterogeneous classification of periarthritis. In the third place, Codman described the clinical picture of frozen shoulder with such clarity that its clinical identification and separation from the other groups presented no further confusion. He appears to have been the first to call attention to the benign ultimate prognosis that characterizes the illness. Though Codman's⁸ clinical description of the condition was most complete, the pathologic basis of the ailment was obscure to him, and he frankly admitted as much. Of his large book on the shoulder, only eight pages are devoted to the frozen shoulder, and he wrote: "These are common cases, but it does not take a long chapter for me to tell all I know about them." Codman believed that the cause of these painful shoulders lay in a "tendinitis of the short rotators," though he confessed this to be essentially a "hunch," and operation on several patients had revealed only "congestion in the floor of the bursa and occasional adhesions."

It was by exclusion, therefore, that periarthritis finally assumed the proportions of an entity. The identification of the disease due to calcific deposits in the shoulder left a large residue of cases of pain in the shoulder in which calcium deposits were not encountered. When the cases of rupture of the supraspinatus tendon were withdrawn from this residue, the greater number of those remaining could be classified as conforming to the clinical syndrome of periarthritis.

Coincident with Codman's clinical studies in Boston, interesting observations were being made by A. W. Meyer of Stanford University.⁹ In the course of routine anatomic dissections of the shoulder, Meyer noted what he termed "attrition" lesions involving the long head of the biceps and the tissues in its vicinity. Thinning, fraying and fibrillation of the tendon were encountered with frequency (7 of

5. Mumford, E. B., and Martin, F. J.: Calcified Deposits in Subdeltoid Bursitis, *J. A. M. A.* **97**:690-694 (Sept. 5) 1931.

6. Dickson, J. A., and Crosby, E. H.: Periarthritis of the Shoulder: Analysis of Two Hundred Cases, *J. A. M. A.* **99**:2252-2257 (Dec. 31) 1932.

7. Michetti, G.: Contributo allo studio della periartrite spontanea della spalla, *Minerva med.* **2**:198-203, 1940.

8. Codman, E. A.: *The Shoulder*, Boston, The Author, 1934.

9. Meyer, A. W.: (a) Unrecognized Occupational Destruction of the Tendon of the Long Head of the Biceps Brachii, *Arch. Surg.* **2**:130-144 (Jan.) 1921; (b) Spontaneous Dislocation of Long Head of Biceps Brachii, *ibid.* **13**:109-119 (July) 1926; (c) Spontaneous Dislocation and Destruction of the Tendon of Long Head of Biceps Brachii, *ibid.* **17**:493-506 (Sept.) 1928.

60 cases).^{9a} Dislocation of the tendon out of the bicipital sulcus as well as complete destruction and separation of its ends was encountered, sometimes with the formation of a new attachment of the distal tendon somewhere in the vicinity of the bicipital groove. These findings were attributed by Meyer to friction of long-continued overuse in the position of abduction and external rotation, and he wondered why "Such cases apparently do not appear in clinics and dispensaries, for pathologists and orthopedic surgeons seem to be unfamiliar with them."^{9a} In a study of 150 routine specimens from the shoulders of cadavers Horwitz¹⁰ confirmed Meyer's findings. He found flattening, fraying and fibrillation of the tendon in 30 instances. Four complete tears were noted. Subsequent to Meyer's studies, Gilcreest pursued a clinical investigation of the subject.¹¹ Gilcreest's observations covered 100 cases of rupture of the long biceps tendon. He recognized the clinical occurrence of a "latent" as well as an acute type, and stated that the former is generally unrecognized, or is diagnosed by the attending physician as sprain, arthritis, bursitis, etc. Gilcreest did not share Meyer's opinion that the condition was caused purely by attrition and spoke of senility, arthritis, myositis, arteriosclerosis, acute and chronic infections, neoplasms, physiologic predisposition, occupation, fatigue and trauma as possible causes.

That these changes in the tendon may represent the sequelae of tenosynovitis was apparently not considered by most writers on the subject, although Ewald¹² did suggest tenosynovitis as the cause of rupture of the long biceps tendon. In this country, tenosynovitis of the long biceps tendon has been vaguely referred to for many years. Codman recollected that he had heard the diagnosis made frequently when he was at medical school, but said that it was employed to describe a pain on moving the elbow up and down, a motion which plainly does not cause the biceps tendon to move. Codman doubted the existence of the lesion, saying that he had never demonstrated it clinically, at operation or at autopsy. At complete variance with this view is that of Pasteur¹³ in France, who described a syndrome of pain and stiffness in the shoulder which he ascribed to *téno-bursite bicipitale*, a new entity. Pasteur did not believe the condition to be very common and expressed confidence in the response of the lesion to faradization. Several years later, Schrager¹⁴ restated Pasteur's findings in what I believe to be the first report of tenosynovitis of the biceps tendon in the American literature. Full credit was given to Pasteur for the original description of the ailment. Schrager expressed the opinion that it was the most common cause of periarthralgias about the shoulder. Diathermy was considered to be almost specific therapy. Neither Pasteur nor Schrager had had opportunity to confirm the presence of the lesion either surgically or by autopsy. The evidence presented in this paper supports the major contention of both Pasteur and Schrager.

10. Horwitz, M. T.: Lesions of the Supraspinatus Tendon and Associated Structures. Arch. Surg. **38**:990 (June) 1939.

11. Gilcreest, E. L.: Rupture of Muscles and Tendons, J. A. M. A. **84**:1819-1822 (June 13) 1925; Subcutaneous Rupture of Long Head of Biceps Flexor Cubiti, S. Clin. North America **6**:547-554, 1926; Dislocation and Elongation of Long Head of Biceps Brachii, Ann. Surg. **104**:118-138, 1936.

12. Ewald: Bizepsriss und Unfall. München. med. Wchnschr. **74**:2214-2215, 1927.

13. Pasteur, F.: La téno-bursite bicipitale, J. de radiol. et d'électrol. **16**:419-426, 1932; Sur une forme nouvelle de périarthralgie et d'ankylose de l'épaule, ibid. **18**:327-328, 1934; Ténobursite bicipitale, Presse méd. **41**:142-143, 1933; La téno-bursite de la longue portion du biceps, Gaz. d. hôp. **107**:477-479, 1934.

14. Schrager, V. L.: Tenosynovitis of the Long Head of the Biceps Humeri, Surg., Gynec. & Obst. **66**:785-790, 1938.

PERIARTHRITIS CLINICALLY

Occurrence.—Periarthritis is in my experience the most common ailment of the shoulder. It is the most frequent, not only in private practice but also in the hospital outpatient department, an incidence which shows that neither the working nor the leisure class is spared. Records reveal its greater frequency in women (65 per cent) and its occurrence chiefly on the right side (72 per cent), the latter observation suggesting the predisposition of the shoulder getting the hardest usage. Two of 3 cases have occurred between the ages of 40 and 60, though the condition has been observed as early as the late twenties and as late as the early eighties. Worthy of comment is the not uncommon occurrence of "frozen shoulder" as a complication of pulmonary and cardiovascular disease, a fact which supports the contention that general debility or attrition may play a role in its etiology. The onset is generally insidious, but in about 1 of 3 cases a clearcut history of trauma is obtained.

Clinical Picture.—The typical history is that of a mild ache in the involved shoulder, often projected down the outer aspect of the upper part of the arm. In the beginning, pain is usually noted only at the limits of normal motion. Sometimes the condition is aborted at this stage after a few weeks and leaves no clinical sequelae. In other instances, this status may persist for months or even years without change and then clear up spontaneously. Generally, however, the pain slowly becomes more severe, and the arm stiffer, until the condition wears the patient down through interference with sleep. At first the limit of external rotation is painful. Progressively, as the pain increases, the entire range of motion of the shoulder shrinks, sometimes to such a point that the appearance of fibrous ankylosis is present. At times, a secondary scalenus spasm develops, and the misery of the patient is increased by pain in the neck and in the back of the shoulder. There may also be radiation of pain and tingling down the inner aspect of the arm to the fingers. I have seen the scalenus spasm so severe as to mask completely the pain in the shoulder, so that interpretation of the picture became apparent only during the examination, when restriction of motion was encountered. Occasionally, and possibly owing to the lack of sensitivity of the individual patient, pain is a negligible factor and the patient presents himself with no history of pain, complaining only of stiffness and restricted use of the involved extremity.

The illness pursues its inexorable undulant course, some days better, some days worse, until a point is reached when, inexplicably, the sequence just described reverses itself. The pain becomes more bearable, although no change is noted in the stiffness of the shoulder. Eventually, motion of the shoulder joint gradually improves and, with ups and downs, complete recovery ensues. Characteristic of the illness is the extreme and unpredictable variability of the time element and the curious static periods which may last for months during which neither improvement nor retrogression can be noted. Most patients are well before ten months have elapsed, though the duration of the illness may vary between three months and two and one-half years. I have never encountered a patient with symptoms of more than two and one-half years' duration, nor have I ever seen recurrent attacks in the same shoulder.

Examination.—The amount of pain and stiffness in the involved shoulder varies with the duration and severity of the illness. In early stages, or in mild forms of the disease, the range of motion may be entirely unrestricted, there being pain only at the limits of normal motion. On the other hand, so little motion may be detected in the shoulder that fibrous ankylosis is simulated. Generally, the patients are first seen at some point between these extremes. Characteristic of the late stages are

the freedom of motion and absence of pain when the shoulder is moved within the limits of its restricted arc. Only when these limits are forced does the typical excruciating pain manifest itself. As Schragger has pointed out, exquisite tenderness over the bicipital groove is invariably present, though the patient is generally surprised at the location of the tender area. I have found the following sign to be equally reliable. With the elbow actively flexed to a right angle so as to produce tension in the biceps mechanism, the thumb of the examiner identifies the long biceps tendon about 3 inches (6.6 cm.) below the joint. The structure is pushed gently to one side and then allowed to slip back to its normal position. As this occurs, a twinge of pain is felt in the involved bicipital groove. Yergason's sign¹⁵ has not been found reliable, an observation which indicates that *motion* rather than *tension* of the tendon produces pain. In cases of long-standing disability, there is flattening of the shoulder because of deltoid atrophy, and the roentgenogram, which is otherwise normal, may show marked globular atrophy about the greater tuberosity, as well as spotty atrophy of the Sudeck type involving the entire humerus.

In the clinical examination, two important differences stand out between the pain due to peri arthritis and that due to calcific deposits. I refer first to the absence of tenderness laterally over the insertion of the supraspinatus or infraspinatus muscles, and secondly, to fixation of the shoulder, not by painful spasm, but by a much less painful block suggesting mechanical obstruction.

MECHANISM

The long head of the biceps, like the appendix, is an unimportant vestigial structure unless something goes wrong with it. Its function as an abductor of the arm is certainly redundant, and sufficient evidence has accumulated to show that its role in holding the head of the humerus against the glenoid cavity is equally dispensable. A few aspects of relevant anatomy will help to clarify its potentialities as a handicap to function of the shoulder when it fails to operate normally.

The biceps "sheath" differs from a true sheath by being closed only at the lower end. It is therefore really a pouch or sac extruded from the shoulder joint. The lining of the joint extends down the bicipital sulcus for about 2 inches (5 cm.). At this point it reflects loosely onto the tendon itself and returns. It adheres to the tendon in its course through the bicipital groove and across the joint, as far as its insertion above the glenoid cavity. Although the cuff is tight where the tendon emerges from the cavity in the joint, the tendon glides freely through it, so that when the arm is in the position of full abduction, scarcely $\frac{1}{2}$ inch (1.3 cm.) of tendon remains in the shoulder joint, the remainder being displaced into the groove. Since almost 2 inches (5 cm.) of tendon is in the shoulder joint proper when the arm is depressed and externally rotated, the excursion is a large one. These facts are important because they indicate that the movable tendon cannot properly be said to have two parts, an intracapsular section and a section enclosed by the bicipital groove (Gilcreest¹¹). Moreover, because of the wide excursion of the tendon, it is clear that an inflammatory process originating in the bicipital groove will spread to some extent to the intra-articular tendon and immediate surrounding structures.

Another interesting point about the biceps tendon is that it does not slide in its sheath in response to pull of the muscle to which it is attached. The biceps muscle exerts its force essentially on motion of the elbow joint, and its long tendon,

15. Yergason, R. M. Supination Sign, J. Bone & Joint Surg. 13:160, 1931.

although tensed, remains immobile. Motion of the long biceps tendon with reference to the humerus is passive and occurs only when the shoulder joint is moved. These facts were studied in the cadaver and on the operating table, and the following salient phenomena were consistently revealed:

1. No motion of the biceps tendon in the bicipital groove can be produced by contraction or relaxation of the biceps muscle if the shoulder is held immobile in any position.
2. Conversely, any motion of the shoulder joint entails motion of the biceps tendon in the bicipital groove.
3. Elevation of the arm in internal rotation causes minimal excursion of the biceps tendon; in external rotation, maximum excursion



Fig. 1—*A*, position of arm producing minimum length of intra-articular tendon *B*, position of arm producing maximum length of intra-articular tendon

4. The greatest excursion of the biceps tendon is produced when the following positions are alternated. (*a*) The tendon is drawn from above into the groove by elevation, internal rotation and forward flexion (fig. 1 *A*) (*b*) The tendon is drawn into the groove from below by backward flexion and external rotation with the arm depressed (fig. 1 *B*).

It is apparent from these data that if the extremes of motion of the biceps tendon in the bicipital groove are painful, motion of the shoulder will also be painful at the limits as noted. If all motion of the biceps tendon in the bicipital groove are painful, all movement of the shoulder will be equally so. Moreover, there is no reason why, under the circumstances, any interference with function of the elbow should occur.

SURGICAL INVESTIGATION

To determine whether tenosynovitis of the long biceps tendon was actually present in so-called "periarthrits," it was considered justifiable to subject a number of typical patients to surgical exploration. The operative procedure was standardized and was carefully carried out, so that no important structures of the periphery of the joint could be neglected.

Through a $2\frac{1}{2}$ inch (6.5 cm.) incision splitting the deltoid muscle (fig. 2) the bursa was entered slightly lateral to the bicipital sulcus and inspected for adhesions

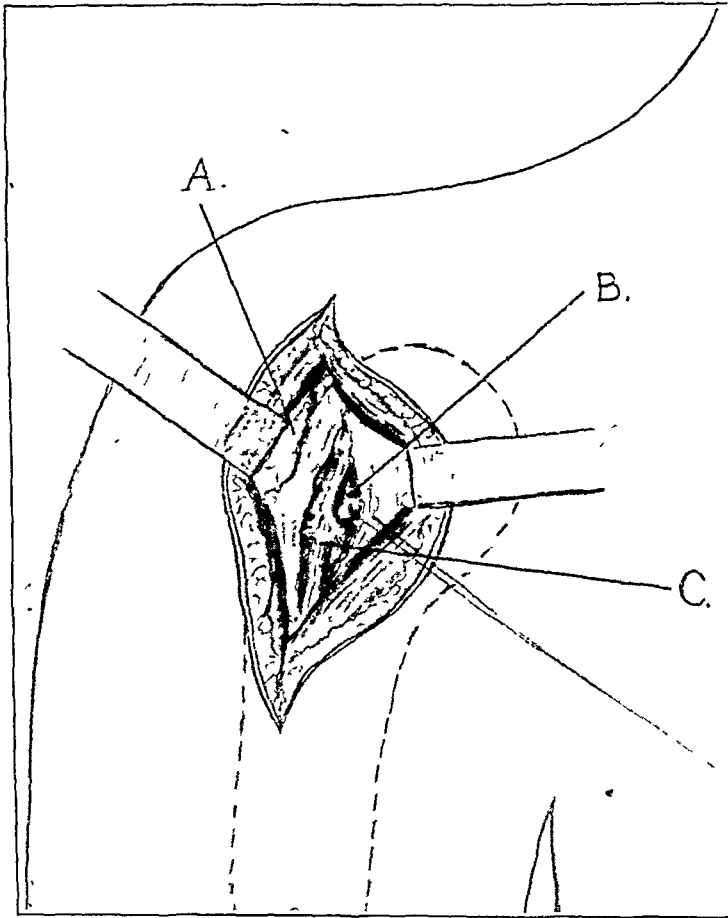


Fig. 2.—Typical appearance of involved structures in severe "frozen shoulder": *A*, glistening, normal-appearing subacromial bursa; *B*, thickened, edematous tendon sheath; *C*, adherent, frayed and roughened long biceps tendon.

and other inflammatory changes. By inward rotation of the humerus, the floor of the bursa and the underlying musculotendinous cuff were inspected. The arm was then rolled back to neutral position to bring the bicipital sulcus into the wound, and in its lower portion a half-inch (1.3 cm.) nick was made in the sheath, exposing the tendon. Flexion and extension of the shoulder were then cautiously performed through the unrestricted arc and the tendon inspected for motion in its sheath. The sheath was then completely split open through the intratuberosus notch, to expose the tendon as far as its entrance into the joint proper. Again the shoulder was gently moved while the tendon was observed to determine its

freedom of motion. If the tendon did not move when inspected through the slit but was free when the sheath had been completely opened, the restriction was considered referable to stenosis, such as is encountered in de Quervain's disease, and not to adhesions. Sections of tendon sheath were then excised for microscopic study. The subsequent procedure will be described hereinafter.

The pathologic conditions encountered in 12 shoulders explored according to the plan just outlined are presented in the accompanying table.

Gross Findings.—Noteworthy was the universal finding of tenosynovitis involving the long biceps tendon, the character and extent of involvement corresponding roughly with the stage of the illness at the time of operation.

Cases 1, 2, 9 and 11 were instances of a relatively mild phase of the illness. Although all 4 patients had been severely incapacitated by pain for a long period, clinical examination revealed a minimum of stiffness, and pain could be produced only at the limits of normal motion of the shoulder. Exploration of the shoulders disclosed in all of them some restriction of motion of the biceps tendon in the groove. Although filmy adhesions were encountered in 1 (case 1), all the tendons moved freely once the sheath was split open completely, and the limitation was accordingly attributed to constriction of the sheath. Gross inflammatory changes were encountered, but they were not extensive. Microscopically, sections of the tendon sheath failed to show the hyaline changes that characterize de Quervain's disease but did show inflammatory changes which differed in no essential manner from those encountered in other explorations.

In cases 5, 6, 7, and 12 the disease was clinically more severe than in the aforementioned cases. Moderate stiffness was present on preoperative examination, but the picture was dominated by excruciating pain and tenderness over the bicipital sulcus. Exploration in these patients disclosed tendons bound down to their sheaths with many thick adhesions. The sheaths were reddened, edematous, thickened and extremely vascular. The tendons themselves appeared dull and discolored. Roughness and some fraying were encountered in 3 cases. In 1 (case 5) free fluid was encountered in the sheath, and in another (case 12) the gliding mechanism had been so injured that tendon and sheath constituted a single swollen mass.

Cases 3, 4, and 10 were representative of a still more advanced lesion. Although the patients had all been through a long period of excruciating pain, at the time of operation stiffness was the outstanding symptom revealed by the examination, and neither the pain nor the tenderness in the bicipital groove was as severe as in the patients in the previous group. On exploration, these shoulders revealed less gross evidence of inflammation than characterized the preceding group. Although some vascularity and edema were encountered, the picture was predominantly that of thick, heavy fibrosis. The sheaths were thickened and fibrotic, and the tendons were firmly glued to them with strong adhesions. When freed from surrounding adhesions, the surfaces of the tendons were irregular, roughened, frayed and fibrillated. Patient 8 showed the most advanced changes encountered in the entire series, and it is unfortunate that the history obtained was not a reliable one. Pre-operative examination revealed free passive motion, but weakness of active abduction. Tenderness of the biceps muscle and the biceps sign were present. Exploration revealed thickening and adhesions in the subacromial bursa and a complete tear of the musculotendinous cuff. The biceps tendon had become firmly attached to the bicipital groove, and its intra-articular section had completely disappeared except for a small stub remaining attached to the glenoid tubercle.

Summary of Data on Twelve Patients Submitted to Operation

Case; Name; Age	Sex; Date; Age	Duration	Trauma Injury	Symptoms and Signs					Gross Operative Findings					Appearance of Tendon Sheath
				Pain At normal limits	Stiff- ness 0	Tender- ness ++	Bicipital Sign ++	Sec- ondary Swelling 0	Reent- rogen- gram Negative	Bursa Negative	Musculo- tendinous Cuff Negative	Teno- synovitis +-	'Frozen' Tendon Sheath Limited motion	
1 J. de la F. May 1940	M 23	1 year	Injury	At normal limits	0	++	++	0	Negative	Negative	Negative	+	Slight motion	Thickened, slight edema; no increased vascularity
2 D. P. Aug. 1940	M 29	2 years	Injury	At normal limits	0	++	++	0	Negative	Negative	Negative	+	Limited motion	Marked thickening and fibrosis; vascularity not increased
3 J. de S. Aug. 1940	M 36	6 months	Chronic	+	++	++	++	0	Negative	Reddening; local adhesions	Negative	+++	Limited motion	Moderate thickening and fibrosis; some edema
4 R. S. Nov. 1940	M 54	6 months	Heavy labor	+	+++	++	++	+	Moderate atrophy	Slight thickening	Negative	+++	+	Slightly increased vascularity; marked thickening and fibrosis; no edema
5 J. R. Dec. 1940	M 33	4 months	Chronic	+	++	++	++	+	Moderate atrophy	Thickened, reddened	Negative	+++	+	Vascular, thickened and edematous; fluid in sheath
6 H. C. March 1941	M 59	10 months	Chronic	+++	++	+++	++	0	Marked atrophy	Local adhesions	Negative	+++	+	Extremely vascular; markedly thickened and edematous
7 H. C. March 1941	M 59	2 months	Chronic	+++	+	++	++	+++	Negative	Local adhesions	Negative	+++	+	Extremely vascular; markedly reddened, thickened and swollen
8 P. I. Oct. 1942	M 56	4 months	Heavy lifting	+	+	++	++	0	Marked atrophy	Adherent	Complete tear	+++	+	Sheath and tendon bound down in large inflammatory adherent mass
9 M. M. Aug. 1942	F 32	1 month	Injury	At normal limits	0	++	++	0	Negative	Negative	Negative	+	+	Slight thickening and increased vascularity
10 A. B. Oct. 1942	F 54	9 months	Chronic	++	+++	++	++	0	Marked atrophy	Locally inflamed	Negative	+++	+	Edema and marked hypervascularity and thickening
11 J. S. Nov. 1942	M 46	2 months	Chronic	++	0	++	++	0	Slight atrophy	Negative	Negative	+++	Moderate motion	Marked thickening; many adhesions; fluid in sheaths; edema
12 R. K. Dec. 1942	F 51	6 months	Chronic	++	+++	++	++	+	Negative	Negative	+++	+	Vascular, thickened and bound to tendon in an indistinguishable mass

Microscopic Appearance.—In almost all of the aforementioned cases, sections of the tendon sheath were removed and subjected to microscopic examination. The changes exhibited in these sections were essentially so uniform that they may be considered together. Inflammatory infiltration, increased vascularity and advanced hyperplasia characterized all of them. Spotty areas of leukocytic and lymphocytic infiltration were common, as well as edema, infiltration into the blood vessels, synovial degeneration and degeneration of collagen fibers. Proliferative changes, present in all specimens, were predominant when the disease was well advanced. Heaping up of the synovial elements and fibroplastic activity were noticeable. In only 1 instance (case 3) was hyaline degeneration noted suggestive of the picture described by de Quervain as characteristic of tendovaginitis at the radial styloid. For obvious reasons, sections of tendon proper were not obtained.

Summary of Observations at Operation.—Pathologic study of these 12 cases of peri arthritis showed that tenosynovitis of the long biceps tendon was present in all. In only 1 instance was a rupture of the musculotendinous cuff encountered, and in no case was any significant change encountered in the subacromial bursa or other periarticular tissues. Only two interpretations of these data appear plausible. Tenosynovitis of the long biceps tendon can represent either an extremely common incidental finding or a basic element of the disease. The normal-appearing and mobile tendons encountered in the course of numerous explorations preparatory to the Nicola and related procedures indicate that the former possibility may be excluded. It is therefore reasonable to infer that tenosynovitis of the long biceps tendon constitutes the underlying pathologic basis of at least most cases of so-called peri arthritis.

COMMENT

The demonstration of tenosynovitis as a consistent finding in so many frozen shoulders brings up a few points for discussion. In the first place, these surgical experiments have shown the term peri arthritis, at least in the sense in which it was used by Duplay, to be inaccurate. The term "frozen shoulder" remains applicable only to the more severe forms. Accordingly, it is proposed that the pathologically descriptive name bicipital tenosynovitis be employed for the condition.

Perhaps of greater importance is the insight gained from this study into the pathologic mechanism which accounts for the inevitable spontaneous clinical recovery. When the operative findings are arranged in the order of the severity of the preoperative clinical picture, it becomes evident that the inflamed biceps tendon becomes more and more adherent to its sheath until it is solidly anchored to it. The inflammatory reaction, extensive while the tendon is still mobile, gradually subsides and finally disappears as the fixation of the tendon to the surrounding tissues becomes firm. It is worthy of note that in the later stages of the disease almost complete fixation and diminishing inflammation were observed before the termination of the period of increase in the severity of symptoms, to which our surgical investigations were necessarily confined. Solid anchorage of the tendon to the bicipital groove, therefore, may be assumed to coincide roughly with the clinical stage at which pain subsides and motion of the shoulder commences to improve. In other words, spontaneous improvement begins when solid and painless fixation of the tendon to its sheath has been achieved.

No opportunity to observe subsequent pathologic changes was presented in these cases, but the previously described postmortem material of both Meyer and Horwitz contained specimens which no doubt represented sequelae of this condition. These specimens indicated that fixation of the tendon to the lesser tuberosity

remains permanently, and this contention is supported clinically by the fact that recurrences of frozen shoulder are not encountered. Moreover, it appears that the intra-articular section of the tendon, no longer useful, becomes attenuated and finally disintegrates. In Horwitz' 4 examples of complete tear the distal portion of each tendon was found attached to the lesser tuberosity. The proximal tendon in 1 had completely disappeared. In 2, only a small stub remained attached to the glenoid tubercle and in the fourth, the proximal portion had become attached to the articular surface of the humerus.

In résumé, then, it is possible to reconstruct the pathologic sequence underlying typical frozen shoulder as follows: The condition is initiated by a mild tenosynovitis gradually becoming more severe, and with adhesions which become more and more firm. During this process, the shoulder becomes progressively stiffer. Once the adhesions become sufficiently solid to anchor the tendon firmly at the intertuberosus groove, pain diminishes and increased motion of the shoulder commences. Return of normal function in the shoulder coincides with the subsidence of inflammatory reaction, which is followed by disintegration of the intra-articular tendon.

It has been stated that the mechanism described refers to "typical" frozen shoulder. Every tenosynovitis of the biceps tendon does not pursue this typical clinical or pathologic course. That the process may be aborted at an early stage is indicated clinically by mild attacks of very short duration which are prone to recurrence, and pathologically by a frayed and fibrillated but nonadherent tendon, also described by both Meyer and Horwitz as commonly observed at postmortem examination.

The exact mechanism by which tenosynovitis of the long biceps tendon produces restriction of motion in the shoulder has presented a perplexing problem. It is plain that when the tendon is frozen to the humerus in neutral position, adduction and external rotation at the shoulder should be limited by tension of the intra-articular tendon itself. Elevation and internal rotation, however, should relax intra-articular tendon, and since these motions are blocked in "frozen shoulder," the cause of the block must be sought elsewhere. The explanations that suggest themselves may be listed as follows:

1. Adhesive subacromial bursitis. ✓
2. Contracture resulting from long-standing voluntary immobilization.
3. Mechanical block caused by infolding of redundant intra-articular tendinous extension.
4. Peritendinous adhesions extending upward into the joint, binding the tendon to the capsule and musculotendinous cuff above and to the articular surface of the humerus below.

Although in the past frozen shoulder has been attributed to adhesive subacromial bursitis, this condition was encountered only once among the 12 patients who were operated on. Apart from occasional insignificant adhesions in the vicinity of the bicipital sulcus, the subacromial bursae in the 11 other patients were normal in appearance. This hypothesis, therefore, is untenable and may be discarded. The theory that a true contracture of the joint results from long-standing immobilization is not reconcilable with my experience in the operating room. In the frozen shoulders operated on, resistance to shoulder abduction persisted until the peritendinous adhesions were freed. As soon as this was accomplished, full motion of the shoulder was possible without forcing and with only the slightest palpable resistance. These observations are incompatible with a generalized contracture at

the joint and indicate rather a localized mechanical block in the immediate vicinity of the area of tenosynovitis. Two possible hypotheses appear compatible with these findings. The first is that the adhesions of the tendon to the sulcus cause the intracapsular portion to buckle downward when the arm is abducted. In this manner, a mechanical block is established similar to that caused by a displaced meniscus in the knee. Surgical release of the adhesions permits the tendon to slide down in its groove when the arm is abducted or internally rotated so that the block disappears. This hypothesis was proved incorrect by the following experiment: After the tendon had been liberated from the groove and the return of normal motion in the shoulder joint had been demonstrated, resuture of the tendon to the groove was performed. No block to motion of the shoulder reappeared. It seems, therefore, that stiffness of the arm is most reasonably attributable to the other possibility, namely, an upward extension of the tenosynovitis into the joint, so that the intra-articular tendon is "frozen" to the capsule above and to the articular surface of the humerus below. Adhesions in these locations might well account for mechanical fixation of the shoulder, since the tendon runs oblique to the supraspinatus and infraspinatus muscles. The occurrence of such adhesions is not surprising when it is recalled that the upper end of the sheath is patent and that in periarthritis the inflamed tendon glides freely into the joint proper. The limitations of my surgical exposure precluded visualization of such a block, and an exposure extensive enough for this purpose was considered inexpedient; but the foregoing data allow of no apparent alternative explanation. Snaps audible during brisement forcé, then, would appear to represent tears either of intra-articular peritendinous adhesions or perhaps of the attenuated intra-articular tendon itself.

THErapy

Recognition of the pathologic sequence underlying periarthritis provides a guide for the reasonable administration of conservative therapy and suggests also a surgical method for its radical cure. In any consideration of therapy, it is of prime importance to bear in mind the inevitable favorable prognosis of the illness, even when no therapy whatever is administered. The many conservative measures that have been advocated for the treatment of this condition are well covered in the literature of the past three decades (see Codman bibliography¹⁶), and a review of this material is beyond the scope of the present paper. The nature and sequence of the underlying pathologic changes indicate, however, that therapeutic measures must be properly timed if the natural healing processes are to be expedited and not delayed by them. In the early stages, it would seem that too much stress has been laid on electrotherapeusis and insufficient attention paid to rest and immobilization, preferably in the position of abduction. According to my experience with tenosynovitis elsewhere, rest not only relieves pain but sometimes aborts the condition. When the tenosynovitis is too far advanced to permit one to anticipate the latter eventuality, immobilization permits adhesions to form about the tendon without the retardation and pain caused by continual motion. As for manipulation, this procedure is clearly useless before stiffness becomes noticeable, and harmful during the period when adhesions are forming and stiffness is becoming progressively more severe. At this time, manipulation either under anesthesia or gently by exercises serves only to increase pain and disrupt soft adhesions, which inevitably reform. These theoretic considerations have been repeatedly confirmed in clinical practice.

16. Codman,^s pp. 211-213.

In the upgrade or healing stage, when stiffness is subsiding, almost any therapeutic procedure will receive unwarranted credit. During this period manipulation, either with the patient under anesthesia or by repeated gentle stretching, does appear to hasten the return of normal motion, though this is difficult to prove. It seems likely that at this stage the attachments of the tendon to the groove are so strong that they are no longer jeopardized and only intra-articular adhesions, or the tendon itself, are stretched or torn.

Surgical therapy is indicated (general condition of the patient permitting) at any stage of the illness when the condition has remained static for a long period, when progress is unduly slow, or when, for extraneous reasons, a more rapid recovery is desirable. The common concomitance of this condition with preexisting or impending cardiac disease suggests caution in excluding these ailments before operation is advised.

Mention has already been made of the cases of protracted involvement in which stiffness remains in abeyance and in which pain is elicited only at the extremes of normal motion. Exploration in 3 such cases revealed tendons fixed to the sheath, not by adhesions but by constricting tendovaginitis, as in de Quervain's disease. In these cases, release of the constriction provides room for the tendon to resume its normal motion in the groove at the operating table. While this condition does not conform to de Quervain's description of the characteristic histologic picture of tendovaginitis, it would appear that it may be clinically regarded as such, and so treated. Simple release of the constriction followed by loose resuture of the sheath in several cases resulted in prompt cessation of pain as well as in rapid and lasting recovery.

For patients with intractable pain and stiffness, i. e., the typical frozen shoulder, the objectives of surgical therapy is the obliteration of the involved tendon—tendon sheath mechanism. This may be accomplished by one of several procedures that have been described and accepted for other purposes. Of these procedures, the Nicola operation and transplantation of the long head of the biceps to the short head or coracoid process may be utilized but are not recommended. Both operations are more extensive than is necessary and entail a relatively long convalescence. I favor suture of the long head of the biceps to the lesser tuberosity, with the arm in adduction and external rotation. This position insures that the intra-articular tendon will be long enough to permit full external rotation. If the tendon is sutured to the tuberosity with the arm in internal rotation, the shortened structure itself will limit full motion of the shoulder. Through a 2 inch (5 cm.) incision splitting the deltoid muscle the long biceps tendon is freed from the surrounding thickened sheath until it moves freely as the shoulder is moved, hypertrophied sheath being freely excised. With the arm in adduction and moderate external rotation, several firm silk sutures are inserted to anchor the tendon to the lesser tuberosity. A uterine clamp or a towel clip may be useful for perforating the latter structure for this purpose. One or two sutures are then placed at a higher level, so as to anchor the tendon to the soft tissue. These sutures prevent play of the tendon when the arm is rotated. Closure is accomplished in layers, and a Velpeau bandage is employed for several days. Detailed experience in the use of this operation for the treatment of frozen shoulder will constitute the subject of a separate report. Suffice it here to say that pain is almost immediately alleviated, that improvement in motion of the shoulder commences promptly, and that activity may generally be resumed in four to six weeks.

SUMMARY AND CONCLUSION

Periarthritis, or frozen shoulder, is a common disabling illness from which recovery is spontaneous, though its course is protracted and its duration unpredictable. Theoretic considerations have suggested that the basic pathologic condition is a tenosynovitis of the long head of the biceps and its sheath. Surgical exploration in 12 cases showed that this lesion was present in all instances, and that no other pathologic lesion of the periarticular structures was consistently present. These findings indicate that bicipital tenosynovitis is the pathologic basis of periarthritis in at least the majority of instances.

Further studies of the result of these surgical explorations indicate that in typical cases the tenosynovitis is adhesive and results in firm fusion of the tendon with the structures of the bicipital groove. When fusion becomes solid, inflammation subsides. Correlation of this picture with the clinical observations in the cases in which exploration was done indicates that clinical improvement commences as soon as the tendon is firmly fused to the humerus. The reports of other workers on material obtained at autopsy suggest that disintegration of the intra-articular portion of the tendon may follow in the period after firm adhesions have developed. This sequence of pathologic events explains how spontaneous cure occurs and why recurrences fail to develop.

The mechanism by which adhesive tenosynovitis produces a frozen shoulder is discussed and various possible explanations evaluated. These studies have cast no light on the basic cause of the condition or on the reason for its frequent comitance with cardiac and pulmonary disease.

On the basis of the pathologic picture and sequence underlying the illness, the merits and timing of conservative therapy are discussed, and a surgical procedure is described for the radical treatment of the condition when rapid cure is desired.

Dr. Paul Klemperer was responsible for the interpretation of the microscopic material.

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PROGRESS IN ORTHOPEDIC SURGERY FOR 1942

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE AMERICAN ACADEMY
OF ORTHOPAEDIC SURGEONS

I. CONGENITAL DEFORMITIES

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Experimental.—The section on congenital deformities in "Progress in Orthopedic Surgery for 1941" opened with an account of Warkany's work on the production of skeletal abnormalities in the offspring of rats fed on a deficient diet. During 1942 he and his associates have reported further on the same work. They¹ point out that it has been asserted often that faulty nutrition of the fetus may be a cause of congenital malformations. The faulty nutrition may have its origin in various disturbances. Faulty implantation of the ovum, diseases of the placenta, interruption of the umbilical blood flow, toxic substances transmitted through the placenta and deficiencies in the diet of the mother have been suggested as causes of deformities in the mammalian embryo or fetus. The last-mentioned cause has aroused new interest in recent years. Warkany and Nelson give the following summary of the work:

1. Skeletal abnormalities occurred in about one third of the offspring of female rats reared and bred on Steenbock and Black's rachitogenic diet no. 2965 supplemented with viosterol (diet I).

2. Similar skeletal defects were not found in the offspring of females of the same strain reared and bred on a stock diet.

3. Similarly no such defects were observed in the offspring of females of the same strain reared and bred on diet II, a diet which differs from diet I in that it contains 2 per cent dried pig liver and only 1 per cent of calcium carbonate.

4. The defects were also absent in the offspring of females reared and bred on diet I supplemented by 2 per cent pig liver only (diet VI).

5. If in diet I the calcium carbonate content was reduced from 3 to 1 per cent, only about one tenth of the offspring showed abnormalities of the pattern of diet I.

6. By alternately breeding the same female on diets I and II, abnormal and normal litters could be produced alternately.

7. The same pattern of abnormalities was obtained in the offspring of rats of two different strains reared and bred on diet I.

8. Apparently a nutritional factor that is absent or inadequate in diet I and present in liver in large amounts is necessary for the normal intrauterine development of the rat.

The frequency of osseous defects in 100 cleared abnormal specimens was found to be as follows²:

Tibia	93	Ulna	50
Mandible	80	Humerus	34
Ribs	75	Hindfoot	31
Fibula	63	Maxilla	8
Radius	58	Scapula	6
Hand	54	Clavicle	6
Sternum	52	Femur	1

A histologic study³ was made of some of the previously described skeletal abnormalities in the offspring of female rats reared on a deficient diet. The

1. Warkany, J., and Nelson, R. C.: Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency, *J. Nutrition* **23**:321-333 (April) 1942.

2. Warkany, J., and Nelson, R. C.: Experimental Production of Congenital Skeletal Abnormalities in Offspring of Rats Fed Deficient Diet, *Am. J. Roentgenol.* **47**:889-892 (June) 1942.

3. Warkany, J.: Skeletal Abnormalities Induced in Rats by Maternal Nutritional Deficiency: Histologic Studies, *Arch. Path.* **34**:375-384 (Aug.) 1942.

abnormal structures examined showed more or less delay in ossification. The orderly relationship between the calcifying cartilage and the osseous parts of the bones was definitely disturbed. Persistence of cartilage was found in areas where ossification should have taken place. The cartilage itself showed signs of abnormal development. The outlines of the structures affected were abnormal in the cartilaginous stage. In early stages of development centers of calcification seen in atypical places explained the abnormal arrangement of the osseous trabeculae found in later stages. It is suggested that a nutritional factor absent in the deficient diet but present in large amounts in liver is necessary for the normal prenatal development of bone in these rats.

Warkany and his associates tried varied diets on different strains of rats⁴ and showed that the addition of iodine, manganese, casein, alfalfa leaf meal and cod liver oil to the diet of females on diet no. I did not prevent abnormalities. The addition of 2 per cent of dried pig liver or of an amount of alcoholic extract of liver equivalent to 4 Gm. for each hundred grams of diet I did prevent all abnormalities. Another series of experiments was carried out to determine the embryologic period in which the malformations are determined. The gestation period of the rat is twenty-two days. Addition of liver before the fourteenth day prevented abnormalities, while after the fourteenth day some abnormalities appeared. This same diet was again tried on three different strains of rats. Two strains survived and one died out on it. The strain which died out produced only 1 offspring, and it was normal. Warkany and his associates believe these observations might be used to refute the conclusion that a given stock is always biologically inferior when congenital malformations appear. In fact, the results of breeding these different strains of rats under adverse environmental conditions indicate that the appearance of malformed offspring rather than none at all may be a sign of hardiness and vigor.

Ehlers-Danlos Syndrome.—Another report appeared in 1942 on the Ehlers-Danlos syndrome. Gordon⁵ reports the case of a 46 year old housemaid who was troubled with splitting of the skin after mild injuries. She and other members of her family were bleeders. Examination of her blood revealed that the bleeding and the clotting time and the number of platelets were normal. There was hyperextensibility of the thumbs of each hand, and the skin was hyperelastic over the elbows. There were numerous linear scars on the subcutaneous surfaces of both ulnas, extending from the wrists to the elbows. Weber, who had reported earlier cases, discusses this one and expresses the opinion that it is a genuine case of Ehlers-Danlos syndrome, though the three main features were present in only a minor degree. He thinks it is interesting to know that this developmental dysplasia may be present in persons who can be regarded as almost normal. [ED. NOTE: A full discussion of the Ehlers-Danlos syndrome appeared in "Progress in Orthopedic Surgery for 1941."⁶]

Surgical Treatment.—Mowlem⁷ discusses the surgical treatment of various congenital defects, only a few of which are of orthopedic interest. He suggests that syndactyly and polydactyly are best operated on between the second and the fourth year. The small raised hemangiomas with capillaries on the surface, which appear

4. Warkany, J.; Nelson, R. C., and Schraffenberger, E.: Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency: Use of Varied Diets and of Different Strains of Rats, *Am. J. Dis. Child.* **64**:860-866 (Nov.) 1942.

5. Gordon, H.: Ehlers-Danlos Syndrome, *Proc. Roy. Soc. Med.* **35**:263-264 (Feb.) 1942.

6. Progress in Orthopedic Surgery: III. Congenital Deformities, *Arch. Surg.* **45**:653-667 (Oct.) 1942.

7. Mowlem, R.: Surgical Treatment of Congenital Defects, *Proc. Roy. Soc. Med.* **35**:683-684 (Aug.) 1942.

after birth are liable to spontaneous cure. Hemangiomas of the deep-seated, truly cavernous type require treatment with roentgen rays or radium.

Absence of Extremities and Bones.—Killingsworth and Engledow⁸ report the case of a 3 year old child with congenital absence of the four extremities. Ectromelia of the four extremities is one of the rarest of human congenital anomalies. Only 3 cases have been reported in medical literature.

The most plausible explanation of such a phenomenon, in view of the embryology of the human fetus, would seem to be that it is due to defective genes in either or both parents at the time of conception. All one can be certain of is that some pathologic or chemical change occurred at the 5 mm. stage of the fetus, thus preventing the normal development of the future limb buds.

Intrauterine amputations and constriction bands are discussed by Barenberg and Greenberg,⁹ who report a case in which there was anesthesia below the constriction band. They think that the depth of the band on the right leg produced anesthesia. Frequent infections and ulcers, which responded poorly to the usual forms of treatment, were complicating factors. Excision of the constricting ring has been partly successful in restoring the function of the superficial nerves. The prevailing theories of the formation of these bands and amputations are briefly reviewed. The most tenable explanation assumes a localized primary defect in the germ plasm. An instance is cited in which amniotic adhesions produced constricting rings.

Complete absence of the posterior arch of the atlas is reported by Brown,¹⁰ who states:

The atlas here described is completely deficient as to the posterior arch. In the absence of the posterior tubercle of the atlas, the rectus capitis posterior minor muscles had their origin from an unusual bony prominence on the spinous process of the epistropheus. It is difficult to conceive that the substitute attachment of the minor rectus muscles to a more distant bone than is normal would have followed resorption of portions of the arch. Hence, this prominence may represent the posterior tubercle of the atlas, ossified from a separate center and united with the epistropheus.

In the absence of evidence of pathology, and considering the substitute attachment of the muscles named, the interpretation of this specimen as a developmental anomaly seems to be the acceptable one.

Weiler¹¹ reports a case of congenital absence of the odontoid process of the axis. He says that dislocation of the atlas on the axis, complicated by congenital absence of the odontoid process of the axis, should be treated by reduction and operative fusion of these two cervical vertebrae, in order to prevent the damage to the spinal cord which would result from recurrent dislocation. He reduced the dislocation by traction and manipulation and obtained fusion by using a short section of rib, which was split longitudinally and sutured to the first and second cervical vertebrae. Two years have passed since the operation, and active use of the head and neck has caused no further complications.

Total congenital absence of the tibia is said to be the rarest of congenital deformities. A thorough search of the literature revealed only 89 cases. Nutt and

8. Killingsworth, W. P., and Engledow, R.: Congenital Absence of Four Extremities, *Am. J. Dis. Child.* **63**:914-918 (May) 1942.

9. Barenberg, L. H., and Greenberg, B.: Intrauterine Amputations and Constricting Bands: Report of Case with Anesthesia Below Constriction, *Am. J. Dis. Child.* **64**:87-92 (July) 1942.

10. Brown, C. E.: Complete Absence of the Posterior Arch of the Atlas, *Anat. Rec.* **81**:499-503 (Dec. 26) 1941.

11. Weiler, H. G.: Congenital Absence of Odontoid Process of Axis with Atlanto-Axial Dislocation, *J. Bone & Joint Surg.* **24**:161-165 (Jan.) 1942.

Smith¹² report a case of their own and give a follow-up report on Myers' case nearly thirty-five years after treatment. Their patient showed complete congenital absence of the right tibia, with no evidence of primary centers of ossification of the proximal end, of the tibial tuberosity or of the medial malleolus. The fibula was hypertrophied, shorter than normal and straight. The proximal end was displaced posteriorly and the distal end laterally from the astragalus. Attempts were made to place the fibula under the femur and over the astragalus by manipulation and casts, and later by operation when the patient was a year old. The fibula could not be held in the desired position, and when he was 5½ years old another operation was done. The leg was still in casts when the report was written. Myers' patient was able to walk with a long leg brace and thought that he had less trouble with his brace than some friends had with artificial limbs. [ED. NOTE.—Their roentgenograms made at the age of 5 show a center of ossification in the position of the proximal end of the tibia. In patients with congenital deformities, since the centers of ossification develop late, neither the tibia nor the fibula should be considered as totally absent until the patient is past 5 years of age.]

Multiple Anomalies.—Furst and Ostrum¹³ report an unusual case, in which there was simultaneous occurrence of three rare developmental anomalies. This patient had platybasia, synostosis of the neck (Klippel-Feil syndrome) and Sprengel's deformity. They state that a common congenital etiologic relation is probable.

Clubbing of the Fingers and Toes.—Clubbing of the fingers and toes has been recognized since the time of Hippocrates as a manifestation of certain forms of intrathoracic disease. Thomas¹⁴ reports a case of clubbing of the digits of unknown cause, but probably of congenital and familial origin. This case represents a borderline situation between acropachy and chronic osteoarthropathy.

Macrodactyly and Peripheral Nerves.—Moore¹⁵ reports 5 cases of macrodactyly, in all of which pathologic changes were found in the peripheral nerves. In 1 (a young adult) the changes were definitely due to a neurofibroma. In the 4 others (all young children) the changes were an increase in endoneurial fibrous tissue, with evidence of degenerative changes in nerve fibers. Three of the 4 children showed at least some of the clinical stigmas of neurofibromatosis. It would seem, then, that the changes in the peripheral nerves may represent an early stage in the development of a neurofibroma.

The fact that local hypertrophy is so constantly associated with pathologic changes in the peripheral nerves would seem to indicate that there is a relationship between them. It is believed that the nervous system exerts some controlling action on the process of growth and that the impaired nerves fail in this function, so that uncontrolled or uninhibited growth results. Whether there are changes in the central nervous system which result in the change in the peripheral nerves is not known.

These observations seem to favor the neurogenic theory as the origin of at least certain types of congenital deformities. Moore feels that the investigation of disease

12. Nutt, J. J., and Smith, E. E.: Total Congenital Absence of Tibia, *Am. J. Roentgenol.* **46**:841-849 (Dec.) 1941.

13. Furst, W., and Ostrum, H. W.: Platybasia, Klippel-Feil Syndrome and Sprengel's Deformity, *Am. J. Roentgenol.* **47**:588-590 (April) 1942.

14. Thomas, H. B.: Agnogenic Congenital Clubbing of Fingers and Toes, *Am. J. M. Sc.* **203**:241-246 (Feb.) 1942.

15. Moore, B. H.: Macrodactyly and Associated Peripheral Nerve Changes, *J. Bone & Joint Surg.* **24**:617-631 (July) 1942.

of the peripheral nerves has been somewhat overlooked and that more careful work along this line might be of great interest.

Cystic Osteodystrophy.—A case of congenital localized cystic juvenile osteodystrophy is reported by Adler¹⁶ in a male infant 4 weeks old in whom there had been demonstrated at birth a fracture of the right tibia and fibula, with callus formation, pseudarthrosis and cystic spaces. After six months the process had extended to the hitherto normal fibula of the left leg, with the same picture of cystic spaces in the vicinity of the fracture and pseudarthrotic healing with osteoporosis of the whole bone. The left tibia appeared roentgenologically intact. In the congenitally diseased right tibia and fibula the destruction of normal bone had extended farther, but not by contiguity. Above the described focus a similar one with the same roentgenologic aspect had appeared. Thus far there had been no spontaneous fracture, but there was renewed medullary hemorrhage. This case, then, was one of so-called localized cystic juvenile congenital osteodystrophy with development of pseudarthrosis, in which, in contradistinction to observations reported in the American literature, the process involved not only the tibia but the right and the left fibula as well.

Clubfoot.—Thomson¹⁷ urges the use of Denis Browne splint for the treatment of congenital clubfeet. He has treated 60 patients in two and a half years, and had only 1 recurrence, and that was the fault of the parents, who abandoned the care of the feet. He prefers to start treatment during the first month of life, usually at about 3 weeks of age. The oldest untreated patient was 1 year of age. Thomson gives the following outline of his method:

The principle of treatment for the correction of deformity is to strap the feet to the splint, which has a connecting cross bar, and then let the infant correct its deformity by incessant kicking. For the sake of convenience, the treatment is divided into four phases (assuming that it is started during the first few weeks of life):

(1) The phase during which the deformity is corrected and carried into over-correction (usually five to six weeks' duration).

(2) The phase of maintaining the correction in the same adhesive splints (approximately five months or even less, if the feet are large enough).

(3) A further period of maintaining correction by the use of boot splints (about six months' duration or until walking commences).

(4) The period during which the boot splints are used as night and resting splints, and supplemented with special walking boots during the active periods of the day. The duration of this phase will have to be decided upon in the future, but should be carried on for at least two to three years.

[ED. NOTE.—After having treated personally about 500 clubfooted children in the last nineteen years, I (J. H. K.) was very anxious to try a method which gave only 1 recurrence in 60 cases, and this the fault of the parents. With casts and wedgings I have not been able to get the percentage of recurrences below 10 to 15 per cent. After I had seen the method demonstrated by Dr. Thomson I obtained all three sizes of splints and tried it on 5 young clubfooted babies. At first it seemed to be an answer to a busy surgeon's prayer. Attention was given to every possible detail, in an effort to get the results claimed, but these could not be obtained. I was unable to correct all of the forefoot adduction. Fastening the feet to the cross bar in an outwardly rotated position caused an outward rotation of the entire leg. As the child attempted to rotate the leg inward to resist this, there was some twisting in the knee joint and in the ankle joint. The splint rotated the astragalus

16. Adler, K. J.: Congenital Localized Cystic Juvenile Osteodystrophy, *Röntgenpraxis* 13:258-262 (July) 1941.

17. Thomson, S. A.: Treatment of Congenital Talipes Equinovarus with Modification of Denis Browne Method and Splint, *J. Bone & Joint Surg.* 24:291-298 (April) 1942.

outward from under the tibia as far as the mortice between the malleoli would permit. The first deformity in the clubfoot to be corrected is the forefoot adduction. This deformity occurs between the forefoot and posterior foot, chiefly in the midtarsal joint. This deformity may be slightly corrected as the foot is strapped to the metal splint, but no further correction can be obtained by rotating the splint outward.

When the cross bar is bent to force the feet up in dorsiflexion, they are brought up in too much valgus, and bad flatfeet are produced. With casts and wedgings, the feet can be brought up in dorsiflexion and still be maintained in the normal position in the midline. In this way the achilles tendon is more thoroughly stretched. The photographs illustrating Thomson's method show the feet in an undesirable amount of valgus. The object of treatment is to produce as nearly normal feet as possible and not severe flatfeet. It is claimed that as the child extends one knee in kicking it will flex the other and thereby stretch the achilles tendon. My patients learned to kick both feet at the same time and avoided this stretching. The 5 children were treated in the hospital where they could be observed, and the nurses thought that they were more "fussy" and not as comfortable as the children treated with plaster casts. Because of inability to correct all the forefoot adduction, and to dorsiflex the feet in the position desired, all of these children were finally put back in plaster casts to finish the treatment. Even though plaster requires more material, time, labor and trained assistants, the better results obtained in my hands justified the extra effort.]

A series of 15 young children with congenital clubfeet is reported on by Davis.¹⁸ He concludes the article, which contributes nothing new, with the statement, "Treatment must constantly be altered to fit the progress made by each individual, and this certainly cannot be done if the patient is not seen frequently by his doctor." In discussing operations on the bones for the older children he says: "It is a safe rule not to attempt interference of this kind until the child is at least eleven years old. It must be borne in mind that osteotomy sites will not unite without adequate bone." [ED. NOTE: I agree with the author in advising the postponement of operations on the bones until the child is older. However, I wonder if any one has ever seen a nonunion occur after an osteotomy at an early age. Forcible manipulations and operations on the bones at an early age usually cause an undesirable amount of stiffness and fusion, both fibrous and bony.]

Torpin¹⁹ reports the case of a newborn infant with prolapsus uteri associated with spina bifida and clubfoot. He gives a review of the literature which leads to the inference that the spina bifida is the primary etiologic factor in the occurrence of the prolapse. It appears that if certain of the sacral nerves are drawn into the spina bifida, there is a partial or complete paralysis of the musculature of the pelvic floor resulting in secondary atrophy.

Coutts²⁰ recommends nonoperative treatment of clubfoot. He has improved still further the statistics of the Clubfoot Clinic of the New York Orthopaedic Dispensary and Hospital by a modification of the previous technic. The skin of the foot and leg is first painted with tincture of benzoin. This prevents infections of the skin. Elastic adhesive is applied as a series of circular strips. A gap is left

18. Davis, J. B.: Treatment of Congenital Clubfoot in Children, *Northwest Med.* **41**:238-241 (July) 1942.

19. Torpin, R.: Prolapsus Uteri Associated with Spina Bifida and Club Feet in Newborn Infants, *Am. J. Obst. & Gynec.* **43**:892-894 (May) 1942.

20. Coutts, M. B.: Adherent Cast in Treatment of Club Foot, *J. Bone & Joint Surg.* **24**:672-676 (July) 1942.

between the strips at the level of the proposed wedging cuts to avoid wrinkling with the correction. A thin felt strip is affixed by a piece of elastic adhesive to the area where the proximal edge of the wedging cut will impinge. He calls these adherent casts because the elastic adhesive sticks to the skin, and the plaster bandage sticks to the meshes in the outer surface of the elastic adhesive. The plaster cast should be from 2 to 4 mm. in thickness. Older children may use walking irons. The wedging cuts employed leave narrow hinges of plaster at points corresponding to the projection of the axis of the joint which is being corrected. The hinges have proved invaluable in guiding the corrective force along physiologic lines. A retention cast is worn for eight weeks. The mother is taught to manipulate the foot, and a wedge is inserted in the outer border of the heel and sole of the shoe.

Four articles on clubfeet, all of which appeared in 1941, have been translated from the German literature. Müller²¹ presents a study of the sex incidence of congenital clubfoot at the Finkenau Gynecologic Clinic in Hamburg during the period 1914 to 1940. In a series of 81,171 births, there were 107 newborn infants with clubfoot, of whom 61 were boys and 46 girls, a ratio of 57 per cent to 43 per cent. Twenty-three of these, including 8 boys and 15 girls (34.8 per cent; 65.2 per cent), did not survive. If the nonviable infants were excluded, the sex incidence was 53 boys to 31 girls or 63.1 per cent to 36.9 per cent. The striking frequency of spina bifida aperta combined with clubfoot in the nonviable infants suggests that the lethal factor may be related to spina bifida aperta. The evident close relation of clubfoot to spinal anomalies should contribute to a clarification of the present problems relating to clubfoot.

The requirements for an efficient night splint are enumerated by Leun.²² The splint must have a corrective effect on the deformity and prevent return of the foot to a faulty position. It must not require too much intelligence on the part of the parents to apply it. Application should be so simple as to be fool-proof. The splint should be light, so as to hinder as little as possible the movements of the foot. It must be cheap. The author describes a duralumin splint developed from Gocht's splint. An illustration shows the construction and mode of application. Its corrective action and the mode of application are described.

The surgical correction of the talipes equinus factor in congenital clubfoot after nonsurgical preliminary treatment is discussed by Debrunner.²³ In some cases the talipes equinus factor, manifested by contracture of the achilles tendon and by permanent plantar flexion of the tarsus and the ankle, resists the nonsurgical treatment generally used for early treatment of congenital clubfoot. This failure is due chiefly to the marked contracture of a strong tendon and to the shortness of the lever. In such cases after successful correction of outward tilting and adduction, special treatment is required for the talipes equinus factor.

Various procedures have been devised, such as lengthening of the achilles tendon and Schede's procedure. Debrunner has used open tenotomy, which does away with the main obstacle. However, this will not always suffice to give room for adjustment of the talus. For this reason he now directs attention to overcoming the ligamentous obstacles in the vicinity of the capsule of the ankle joint, as earlier advocated by Vulpis. This operation, after preliminary nonsurgical treatment in severe cases, will practically always prevent recurrence and achieve the best possible correction of the deformity. Careful postoperative treatment is of course

21. Müller, R.: Sex Ratio of Incidence in Congenital Clubfoot, *Ztschr. f. Orthop.* **72**:237-250, 1941.

22. Leun, W.: Night Splints in Therapy of Clubfoot, *Ztschr. f. Orthop.* **72**:250-253, 1941.

23. Debrunner, H.: Surgical Correction of Talipes Equinus Factor in Congenital Clubfoot After Nonsurgical Preliminary Therapy, *Zentralbl. f. Chir.* **68**:1613-1616 (Aug. 23) 1941.

necessary with special attention to proper splints, shoes, exercises, etc. The plaster cast can be removed after three weeks.

Thomassen,²⁴ in discussing the causes of congenital clubfoot, says it appears to be but slightly probable that external conditions during pregnancy play any role in its development. The pathogenesis of the deformity has not been fully established, but it seems to involve an inhibitory malformation. He refers to the work of Wisbrun (1932), who sets forth some new points of view concerning the nature of the deformity and its treatment, saying that it involves a supination of the foot. Thomassen has studied the mechanism and anatomy of the deformity and agrees that the congenital clubfoot is a supination deformity with an equinus contracture in the ankle joint. The supination deformity can be analyzed as consisting in: (1) a supination rotation of the foot; (2) an inversion, or inward rotation of the foot as a whole in relation to the talus, and (3) an inflection, or medial and plantar flexion of the foot at the level of the joint of Chopart.

The essential feature of the supination deformity is the supination position of the calcaneus in relation to the talus. The calcaneus is turned round its longitudinal axis in the direction of supination, but at the same time it also turns round a vertical axis, so that its anterior end swings medially and plantarly in relation to the talus (inversion). Owing to its intimate ligamentous connection with the calcaneus, the navicular bone follows it in relation to the talus, so that it turns medially on the head of the talus and the foot is flexed medially in the joint of Chopart (inflection).

The inversion of the calcaneus in relation to the talus brings about the inversion of the foot as a whole in relation to the ankle joint and the leg, so that the foot points medially as long as the supination deformity remains. The amount of inversion of the foot affords a serviceable expression for the degree of the supination deformity.

Dorsoplantar roentgenography of the foot gives an impression of the supination of the tarsus and especially of the inversion of the calcaneus in relation to the talus. The calcaneus and the talus form an angle which in the normal foot of a child is about 35 degrees. In a foot with a valgus deformity this angle is greater than 35 degrees and may be as great as 70 to 80 degrees, while in a supination deformity it is less than 35 degrees, and may even be zero. In comparison with the clinical observations, the diminution of the calcaneus-talus angle corresponds to the clinical inversion.

These features can be demonstrated by pathologic anatomic studies, and it is appropriate here to call attention to "*De anatomia pathologica pedis equini et vari*," a Danish work by Johan Christian Weis, who in 1842 emphasized these very features as essential in the nature of the congenital clubfoot.

Thomassen gives a technic for manual redressment by which the supination deformity may be corrected as well as the equinus. Finally, description is given of an "ideal" retaining bandage. In some cases it has been difficult to preserve the correction of the equinus contracture, so that lengthening of the achilles tendon had to be performed subsequently.

The progress and outcome of the treatment have been controlled clinically and roentgenographically. A "satisfactory correction" is considered to have been achieved when the form and position of the foot are normal and roentgenograms show a mutual position of the bones corresponding to that in a normal foot.

24. Thomassen, E.: The Congenital Clubfoot: The Mechanics of the Deformity and Its Primary Treatment. *Acta orthop. Scandinav.* 12:33-100, 1941.

II. CONGENITAL DISLOCATION OF THE HIP

PREPARED BY DR. A. BRUCE GILL, PHILADELPHIA

There has been little in the literature during the year 1942 on congenital dislocation of the hip. The most important contributions are two articles on dysplasia of the acetabulum.

Goodwin and Cameron²⁵ make a brief review of the literature and discuss the incidence and the signs and symptoms of the condition. They advise reduction by gentle manipulation for children up to the age of 8 years but do open reduction of any dislocation believed to be either irreducible or incapable of being permanently reduced without operation. They employ the shelf operation for reconstruction of the acetabulum and point out, properly, that the shelf should be placed low and should constitute an extension of the roof of the acetabulum over the head of the femur.

Krida²⁶ discusses the incidence, the pathology and the symptomatology of congenital dislocation of the hip. He states that this condition can be cured only in infancy or early childhood. After this period of life has passed there is no treatment that can restore the hip to normal condition. The treatment is by manipulation if possible. If manipulation is not possible, he advises open reduction. If there is considerable anteversion of the neck of the femur he advises a supracondylar osteoclasts after the hip has been reduced and has remained fixed in plaster for three months. He believes that the compensatory correction of anteversion by means of osteoclasts is necessary to prevent redislocation of the hip and that anteversion does not correct itself spontaneously.

Colonna²⁷ makes a late follow-up report on the operation which he first described in 1932. Preliminary traction is employed to pull the head of the femur downward to the site of the primary acetabulum. The hip is exposed at the time of operation by cutting the long head of the rectus femoris muscle and reflecting the great trochanter upward and backward. The isthmus of the capsule is identified and is cut transversely. The proximal portion of the capsule is then sutured together to cover the head of the femur. An excavation is reamed out of the pelvis to hold the head of the femur, which is now completely covered with the capsule. The trochanter is replaced and the wound is closed. The extremity is fixed in a plaster cast to maintain 20 degrees abduction of the hip. Continued traction is employed within the cast. Four weeks later active and passive movements of the hip are begun. In this paper the author reports the end results for 6 patients examined from seven to twelve years after operation. Function in their hips is excellent. He advocates this method of arthroplasty for two types of patients: those under 3 years of age in whom reduction cannot be maintained after closed manipulation, and those between 3 and 10 years of age, for whom it is the method of choice.

Elsner²⁸ reports in detail 2 cases of congenital dysplasia of the hip with spontaneous healing. He emphasizes the fact that the primary lesion in congenital

25. Goodwin, F. C., and Cameron, D. M.: Congenital Dislocation of the Hip (Its Incidence in New Mexico), *Southwestern Med.* **26**:105-108 (April) 1942.

26. Krida, A.: Congenital Dislocation of the Hip: General Considerations and System of Curative Treatment, *S. Clin. North America* **22**:553-563 (April) 1942.

27. Colonna, P. C.: Arthroplasty for Congenital Dislocation of the Hip: Late Follow-Up Report, *J. Bone & Joint Surg.* **24**:812-826 (Oct.) 1942.

28. Elsner, W.: Spontaneous Healing of Congenital Dysplasia of the Hip, *Zentralbl. f. Chir.* **68**:1983-1988 (Oct. 18) 1941.

dislocation of the hip is dysplasia of the acetabulum and the head of the femur. This must be kept in mind when processes of development are being considered. It is the congenital dysplasia which permits luxation of varying degree or goes on to spontaneous healing. Spontaneous healing may occur in the second and the third year. Spontaneous healing of actual dislocations is rare, about 34 cases having been reported in the literature. In the first case reported by Elsner spontaneous healing took place in spite of poor conditions with abrupt declivity of the femoral neck. Care is needed in evaluating the dislocation tendency of a dysplasia, since this cannot always be predicted. In the second case, in which the deformity was bilateral, spontaneous healing occurred on one side, that with initially the apparently worse prognosis. Nagura has observed numerous cases of spontaneous healing of congenital dysplasia and congenital dislocation of the hip, probably because he is a believer in late treatment. It is never justified to postpone treatment in the hope of spontaneous healing, since reduction is much easier in the early stages, even when there is slight dislocation. Elsner prefers to intervene so that the child may recover in time for the normal walking period, even if continence has not yet been attained.

Hart²⁹ stresses delay or persistent defects in the development of the acetabulum (dysplasia) as the primary cause of subluxation and of dislocation of the hip. This dysplasia has a hereditary background. He cites the work of Faber and other authors to prove that dysplasia without dislocation is more frequent than dysplasia with dislocation and that studies of this familial trait should be based on the dysplasia, as shown in roentgenographic studies of all members of the family, rather than on the dislocation. In other words, dysplasia may occur frequently in successive generations, while frank dislocation may be comparatively rare.

A primary congenital dysplasia of the hip may be severe enough to produce dislocation. On the other hand, it may be so slight that it is corrected during the period of growth and the hip eventually becomes normal. If it is of medium severity, some degree of subluxation results.

If the dysplasia is of minor or very moderate degree, clinical symptoms of fatigue, pain and instability of the hip may never arise. In other patients these symptoms may develop only in adult life. The roentgen examination then reveals the incongruity of the hip joint and evidence of a chronic traumatic osteoarthritis of the hip. The symptoms of these patients are due to a partial instability of the hip (subluxation) and to the presence of the arthritis.

The author rightly insists that dysplasia without dislocation is a distinct clinical and roentgenographic entity and that it should be included in textbooks on congenital dislocation of the hip.

[ED. NOTE.—This is a valuable paper. This defect has not received sufficient attention in genetic studies or in follow-up care after reduction of congenital dislocations. Long-continued observation after reduction is essential to determine whether the primary dysplasia will be corrected by natural processes of growth or will persist and eventually result in subluxation of the hip. If the corrective operation for subluxation is delayed until adult life, it may improve or correct the instability of the hip, but it may not relieve the symptoms which are due to arthritis. It is important, therefore, to restore the congruity of the hip early in life, as soon as subluxation becomes evident, to prevent the secondary pathologic processes from developing.]

29. Hart, V. L.: Primary Genetic Dysplasia of Hip With and Without Classical Dislocation, *J. Bone & Joint Surg.* **24**:753-771 (Oct.) 1942.

III. DISEASES OF GROWING AND OF ADULT BONE

PREPARED BY DR. R. BEVERLY RANEY, DURIHAM, N. C.

Interest in this group of relatively rare and obscure diseases of bone has been manifested during the year by an abundance of case reports accompanied by brief reviews of the literature. On the other hand, original contributions evincing progress toward an increased understanding of these diseases have been few. The influence of the war is shown in an increased number of articles on caisson disease, the only disease of this group directly related to conditions of military combat.

Caisson Disease.—At high pressure the atmospheric gases, chiefly nitrogen, saturate the blood and are taken up by the fatty tissues. It is now generally agreed that caisson disease is caused by a too rapid liberation of gas into the tissues during decompression. Of orthopedic interest are the late osseous changes which often develop in caisson workers. The affected bones show areas of aseptic necrosis with fibrous invasion, mottled sclerosis and incomplete replacement by new bone. The cause of these changes is believed to be multiple gas embolisms resulting in infarctions. The changes may be located in the diaphysis or beneath the articular surfaces. Herzmark³⁰ describes a patient who after six years as a caisson worker became disabled by pain in the right shoulder and in both hips. Roentgenographic examination revealed aseptic necrosis in the humeral and femoral heads. Herzmark considers these late osseous changes to be a result of repeated incomplete decompressions. Swain³¹ describes destruction of the articular cartilage of the femoral heads in a caisson worker 37 years old who had had pain in the right hip for nine months and who died of a coronary accident. Swain emphasizes the advisability of prophylactic treatment consisting of slow decompression and recompression, and periodic roentgenographic examinations of the bones. He believes that the incidence of caisson disease will increase because of the widespread use of the submarine and of high altitude flying in modern warfare. Bell, Edson and Hornick³² have demonstrated the roentgenographic changes of aseptic necrosis in 32 workers under conditions of increased atmospheric pressure, none of whom had had symptoms referable to the bones and many of whom had never had "the bends." These investigators believe that the extent of involvement of the various long bones is proportionate to their fat content.

Osteitis Deformans.—Compression of the spinal cord by the thickened vertebrae of osteitis deformans, or Paget's disease, has been described in approximately 20 cases. To this number Gross³³ adds a report on the case of a man 53 years of age whose paraplegia and incontinence were cured by laminectomy at the middle-dorsal level.

Orban³⁴ studied in detail the histologic changes in the sclerotic areas of skulls affected by osteitis deformans. He describes six types of sclerotic bone, which vary distinctly in histologic detail but demonstrate as a group the disordered resorption and new formation of bone characteristic of this obscure disease.

30. Herzmark, M. H.: Bone Changes in Caisson Disease: Report of a Case, *Bull. Hosp. Joint Dis.* **3**:128-133 (Oct.) 1942.

31. Swain, V. A. J.: Caisson Disease of Bone, with Report of Case, *Brit. J. Surg.* **29**: 365-370 (April) 1942.

32. Bell, A. L. L.; Edson, G. N., and Hornick, N.: Characteristic Bone and Joint Changes in Compressed-Air Workers: Survey of Symptomless Cases, *Radiology* **38**:698-707 (June) 1942.

33. Gross, S. W.: Compression of Spinal Cord in Paget's Disease of Vertebrae, *Am. J. Surg.* **55**:575-577 (March) 1942.

34. Orban, B.: Sclerotic Areas in Skulls Affected with Paget's Disease, *Arch. Path.* **33**: 607-618 (May) 1942.

The treatment of osteitis deformans remains unsatisfactory. Taylor³⁵ reports a case in which disabling pain subsided completely after a series of subcutaneous injections of cobra venom. Lyon³⁶ believes intensive vitamin A therapy an essential part of the treatment and reports the case of a patient who was considered to have Paget's disease with a vitamin A deficiency ascribed to hyperthyroidism. A case of osteitis deformans showing metastatic calcification attributed to treatment with viosterol is reported by Wells and Holley.³⁷

Parathyroid Glands, Renal Insufficiency and Bony Changes.—Although its causes remain obscure, primary hyperparathyroidism, characterized by hyperplasia of the parathyroid glands, cystic changes in bones, alterations of the blood chemistry and little or no damage to the kidneys, is a recognized entity. Sherman and Nolan³⁸ add to the literature a case in which one of the parathyroid glands, of normal size when visualized at operation for removal of a hyperplastic gland, was found at autopsy to have become hyperplastic. In this case the electrocardiogram showed the shortening of the RT interval which has been described previously as occurring in hyperparathyroidism. Chasnoff, Friedfeld and Tunick,³⁹ reporting on a patient suffering from acromegaly and hyperparathyroidism, discuss the interrelationship of pituitary and parathyroid glands.

Increasing emphasis on impaired renal function as a factor connected with hyperplasia of the parathyroid glands and with cystic bone changes is evident. Jaffe⁴⁰ summarizes the differential diagnosis of hyperparathyroidism and states that the cases fall into two groups: those of primary hyperparathyroidism, in which the origin of the disease is in the parathyroid glands, and those of secondary or renal hyperparathyroidism, in which parathyroid hyperplasia is associated with a primary renal insufficiency. He states that the patient with renal hyperparathyroidism is usually under 20 years of age. The history is that of stunted growth and symptoms referable to the kidneys, the phosphorus and the phosphatase content of the serum are elevated, and the calcium content is normal or elevated. The treatment consists of measures to improve renal function.

Andersen and Schlesinger⁴¹ have reported 2 cases of renal hyperparathyroidism in infancy. The presenting clinical picture was that of tetany and acidosis. Postmortem examination revealed severe renal damage, hyperplasia of the parathyroid glands, cystic changes in the bones and metastatic calcification of small arteries.

Cases of renal dwarfism, or renal rickets, have been recorded during the year by Graham and Hutchison,⁴² and the subject has been reviewed by Clément.⁴³

35. Taylor, F. R.: Use of Cobra Venom in Treatment of Osteitis Deformans: Report of a Case, *North Carolina M. J.* **3**:244-245 (May) 1942.

36. Lyon, E.: Relation of Osteitis Deformans to Hyperthyroidism, *Schweiz. med. Wchnschr.* **72**:592-596 (May 30) 1942.

37. Wells, H. G., and Holley, S. W.: Metastatic Calcification in Osteitis Deformans (Paget's Disease of Bone), *Arch. Path.* **34**:435-442 (Aug.) 1942.

38. Sherman, C. F., and Nolan, D. E.: Hyperparathyroidism, *Am. J. Roentgenol.* **47**: 882-888 (June) 1942.

39. Chasnoff, J.; Friedfeld, L., and Tunick, A. M.: Hyperparathyroidism in Patient with Acromegaly, *Ann. Int. Med.* **16**:162-175 (Jan.) 1942; correction, *ibid.* **16**:369 (Feb.) 1942.

40. Jaffe, H. L.: Primary and Secondary (Renal) Hyperparathyroidism, *S. Clin. North America* **22**:621-639 (April) 1942.

41. Andersen, D. H., and Schlesinger, E. R.: Renal Hyperparathyroidism with Calcification of Arteries in Infancy, *Am. J. Dis. Child.* **63**:102-125 (Jan.) 1942.

42. Graham, S., and Hutchison, J. H.: Familial Renal Dwarfism, *Arch. Dis. Childhood* **16**:253-256 (Dec.) 1941.

43. Clément, R.: Renal Dwarfism and Renal Rickets, *Presse méd.* **49**:477-483 (April 30-May 3) 1941.

The outstanding manifestations are grave renal lesions and retarded growth. The data in cases of this type are often incomplete, and the exact relationship of renal dwarfism to renal hyperparathyroidism remains obscure.

Pituitary Gland, Thyroid Gland and Growth of Bone.—In one of the few experimental studies in this branch of orthopedics reported during the year, Becks and his associates⁴⁴ observed the effects of thyroxin and anterior pituitary extract on bone growth in rats. In addition to normal animals, the subjects included rats from which the thyroid and parathyroid glands, the pituitary gland or all of these glands had previously been extirpated. The authors conclude that thyroxin and anterior pituitary extract have a synergistic action in promoting growth of bone, and that of the two anterior pituitary extract is the more important.

Fibrous Dysplasias of Bone with Extraskkeletal Changes.—In 1937 Albright and his associates described 5 patients who showed fibrocystic bone changes and areas of brown pigmentation of the skin. Precocious puberty was evident in the female but not in the male patients. The age of onset was early, at or before 10 years, and the first symptom in most cases was a pathologic fracture. The blood chemistry was normal. The name of "Albright's syndrome" has been applied to this condition. In a recent article, Gorham and his associates⁴⁵ state that 49 instances of the syndrome have been reported; to these they add 2 other cases. The cause of this syndrome has not been determined. Albright suggested that it might be a neurologic disturbance or an embryologic defect. White⁴⁶ reports 1 similar case which he believes to be the result of a congenital abnormality in the maturation of fibrous tissue.

In 1938 Lichtenstein reported 8 cases of a similar or possibly identical disease, which he termed "polyostotic fibrous dysplasia." Lichtenstein and Jaffe⁴⁷ have recently described 15 additional cases. Small rarefied lesions appear in roentgenograms of the involved bone or bones, pathologic fracture may occur, areas of pigmentation of the skin are present and precocious puberty takes place in the female. The authors ascribe the syndrome to defective development of the bone-forming mesenchyme.

Osteomalacia.—Of interest in demonstrating a pathogenesis for one type of osteomalacia is a case reported by Miyakawa and Stearns.⁴⁸ The patient, a victim of long-continued steatorrhea, manifested a severe and rapidly progressing osteoporosis accompanied with pathologic fractures. The authors suggest that in this case the chronic steatorrhea impaired the absorption of minerals and of fat-soluble vitamins. After treatment with a low fat diet supplemented with vitamin D, bile salts, pancreatin and calcium lactate, the phosphatase content of

44. Becks, H.; Ray, R. D.; Simpson, M. E., and Evans, H. M.: Effect of Thyroxin and Anterior Pituitary Growth Hormone on Endochondral Ossification; Species Used: Rat, Arch. Path. **34**:334-357 (Aug.) 1942.

45. Gorham, L. W., and others: Albright's Syndrome: Group of Cases Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Gonadal Dysfunction, Clinics **1**: 358-385 (Aug.) 1942.

46. White, E. H.: Polyostotic Fibrous Dysplasia, Surgery **11**:607-623 (April) 1942.

47. Lichtenstein, L., and Jaffe, H. L.: Fibrous Dysplasia of Bone: Condition Affecting One, Several or Many Bones, Graver Cases of Which May Present Abnormal Pigmentation of Skin, Premature Sexual Development, Hyperthyroidism or Still Other Extraskkeletal Abnormalities, Arch. Path. **33**:777-816 (June) 1942.

48. Miyakawa, G., and Stearns, G.: Severe Osteoporosis (or Osteomalacia) Associated with Long-Continued Low-Grade Steatorrhoea, J. Bone & Joint Surg. **24**:429-437 (April) 1942.

the patient's blood dropped to a normal level and her bones regained normal density.

Fragilitas Ossium.—Rudolph⁴⁹ reports a study of the different types of fragilitas ossium, or brittle bones, and their hereditary basis. He describes 4 cases of congenital osteogenesis imperfecta characterized by multiple fractures at birth and severe deformities, 5 cases of osteopsathyrosis idiopathica characterized by spontaneous fractures after birth and 3 cases showing mixed characteristics. From the genetic observations he concludes that a single pathogenesis may underlie both congenital osteogenesis imperfecta and idiopathic osteopsathyrosis.

In a study of recurrent fractures, Evans⁵⁰ points out that many of the patients are children whose bluish scleras and lax ligaments suggest a constitutional background like that of fragilitas ossium.

Osteopetrosis and Osteopoikilosis.—Anthony and Pollack⁵¹ report a case of osteopetrosis, or marble bones, in a Negro girl in whom blindness developed gradually during childhood because of constriction of the optic nerves by narrowed optic foramens; in the same patient a pathologic fracture of the femur occurred at the age of 9 years. Kellogg and Linsman⁵² and McLean⁵³ have reported 3 additional cases of osteopoikilosis, or osteopathia condensans disseminata.

Dyschondroplasia.—During the year, about 42 cases have been added to the literature. Among these is a group of 36 patients with hereditary deforming dyschondroplasia described by B. T. Vanzant and F. R. Vanzant.⁵⁴ These patients were in five generations of a family numbering 78 members, some of whom had intermarried. The disease was transmitted as a mendelian dominant.

Morquio's Disease.—Marcos and Pieroni⁵⁵ report 3 instances, in sisters, of this obscure infantile chondro-osteodystrophy, which has received considerable attention in pediatric journals but little in the orthopedic literature. The disease is characterized roentgenographically by widespread anomalies of epiphyseal ossification and clinically by the gradual development of multiple and severe deformities. The cause has not been established. Marcos and Pieroni state that 45 cases have been reported.

Calcinosis.—Ghormley⁵⁶ reports an interesting and unusual case of multiple large cystic and calcareous masses occurring in bursal areas of the extremities. Two siblings of the patient were similarly affected. Studies of the calcium balance gave negative results. The cause of this condition, which appears to be a form of calcinosis circumscripta, has not been established.

49. Rudolph, S.: Identity of Osteogenesis Imperfecta Congenita and Osteopsathyrosis Idiopathica, *Monatschr. f. Kinderh.* **88**:200-221, 1941.

50. Evans, W. A., Jr.: Recurrent Fracture, *Surg., Gynec. & Obst.* **74**:204-219 (Feb.) 1942.

51. Anthony, B. W., and Pollack, H. M.: Marble Bones with Pathologic Fractures and Bilateral Optic Atrophy in Negro Child, *Radiology* **38**:355-359 (March) 1942.

52. Kellogg, D. S., and Linsman, J. F.: Osteosclerosis Fragilis, Osteopathia Condensans Disseminata: Two Case Reports, *Southwestern Med.* **26**:44-47 (Feb.) 1942.

53. McLean, E. H.: Osteopoikilosis: Disseminated Osteosclerosis, *Northwest Med.* **41**:92-93 (March) 1942.

54. Vanzant, B. T., and Vanzant F. R.: Hereditary Deforming Chondrodysplasia, *J. A. M. A.* **119**:786-790 (July 4) 1942.

55. Marcos, J. R., and Pieroni, L. A.: Dyschondroplasia (Morquio's Disease) with Report of Three Cases in Same Family, *Arch. de pediat. d. Uruguay* **12**:625-648 (Oct.) 1941.

56. Ghormley, R. K.: Multiple Calcified Bursae and Calcified Cysts in Soft Tissues, *Tr. West. S. A.* (1941) **51**:292-308, 1942.

IV. CHRONIC ARTHRITIS

PREPARED BY DR. LORING T. SWAIM, BOSTON

General.—Knowledge of rheumatic disease has increased, and the investigators are constantly following the new leads which present themselves. However, one is confronted with a complex problem which requires an open mind and a critical attitude toward new and untested methods of treatment. As Pemberton and Scull⁵⁷ have pointed out, arthritis is the resultant of many factors and represents the cumulative effects of a "total war," and recovery requires treatment which constitutes "total support." This "total support" means rest and nutrition because of the malfunctioning of many systems, chief among which is the gastrointestinal tract. The diet must be carefully chosen so as not to overload the atonic bowel and to furnish adequate amounts of vitamins, supply the deficiency of protein, correct the anemia and maintain the water balance. There is no routine treatment; all means must be used, including physical therapy.⁵⁸ Freyberg⁵⁹ makes the following statement:

Treatment must be individualized for each patient and should be based upon two main objectives; (1) to establish optimal general health and comfort and to prevent as much as possible deformities and crippling, and (2) to arrest the inflammatory process if possible. Among the general measures, rest, physical therapy, exercises of affected joints, relief of discomfort, adequate nutritious diet, orthopedic measures and correction of associated disorders, such as anemia, are of definite value.

An excellent summary⁶⁰ has been published in *The Journal of the American Medical Association* under the auspices of the American Rheumatism Association. This primer gives the present American conception of arthritis.

Gold Salts.—The interest in gold salts as a means of treating rheumatoid arthritis is increasing. The problem is still to find an effective soluble salt which is not toxic. Cooperative research is in progress.⁶¹ Reports of the satisfactory results obtained with rheumatoid arthritis increase as knowledge of the action, dosage and physiologic handling of the gold compounds increases. Since the dangers are better understood they can be more easily avoided.⁶²

Dawson, Boots and Tyson⁶³ state: "Chrysotherapy offers greater promise than any other form of therapy in the treatment of rheumatoid arthritis. However, the danger of gold salts cannot be too strongly emphasized. In spite of its obvious disadvantages, the continuation of this type of therapy in the hands

57. Pemberton, R., and Scull, C. W.: Generic and Specific Influences of Nutrition in Total Support of Arthritics, *Ann. Rheumat. Dis.* **3**:42-56 (May) 1942.

58. Solomon, W. M.: Physical Therapy in Arthritis, *Arch. Phys. Therapy* **23**:457-466 (Aug.) 1942. Pemberton, R.: Refinements in Treatment of Arthritis Especially in Relation to Physical Therapy, *ibid.* **23**:581-587 (Oct.) 1942. Treusch, J. V., and Krusen, F. H.: Follow-Up Study of Physical Therapy Applied at Home for Arthritis, *Proc. Staff Meet., Mayo Clin.* **17**:524-528 (Oct. 7) 1942.

59. Freyberg, R. H.: Recent Trends in the Treatment of Rheumatoid Arthritis, *Ohio State M. J.* **38**:813-820 (Sept.) 1942.

60. Jordan, E. P., and others: Primer on Arthritis, Prepared by Committee of the American Rheumatism Association, *J. A. M. A.* **119**:1089-1104 (Aug. 1) 1942.

61. Sabin, A. B.: New Gold Salt for Treatment of Rheumatoid Arthritis: Experimental and Clinical Studies, *Proc. Staff Meet., Mayo Clin.* **17**:542-544 (Oct. 21) 1942. Baker, D. M.: Gold Injections in Treatment of Arthritis, *M. Press* **206**:419-421 (Dec. 3) 1941. Cecil, R. L.: Kammerer, W., and dePrume, F. J.: Gold Salts in Treatment of Rheumatoid Arthritis: Study of Two Hundred and Forty-Five Cases, *Ann. Int. Med.* **16**:811-827 (May) 1942.

62. Freyberg, R. H.: Block, W. D., and Wells, G. S.: Gold Therapy for Rheumatoid Arthritis: Considerations Based upon Studies of Metabolism of Gold, *Clinics* **1**:537-670 (Oct.) 1942.

63. Dawson, M. H.; Boots, R. H., and Tyson, T. L.: Gold Salts in Treatment of Rheumatoid Arthritis, *Tr. A. Am. Physicians* **56**:330-338, 1941.

of careful clinicians is both desirable and justifiable." Nothing, however, gives the striking improvement associated with pregnancy or with jaundice. Without repeated laboratory studies of the blood and urine, it is dangerous to give a gold compound.⁶⁴ Judicious administration of small doses of a gold salt is strongly recommended, since its excretion is slow and danger lies in too rapid accumulation of gold in the body.⁶⁵ Even when caution is exercised gold therapy remains extremely dangerous, and the delayed toxic effects may be fatal.⁶⁶

[ED. NOTE.—There is mention in the German literature of a copper preparation which is said to be superior to gold for chronic rheumatoid arthritis.⁶⁷]

Gout.—Numerous papers⁶⁸ have been written about gout, because apparently after having had a period of neglect, the disease is being found again and studied more carefully, with better understanding. Hereditary factors are important and are often overlooked.^{68a} It is important to investigate relatives of gouty patients for hyperuricemia. In one family, the father and all three sons had gout. Gout is rare in Negroes. In 2 cases reported by Cohen^{68b} the patients were found to have several white ancestors. Treatment during the acute stage consists of rest, medication with colchicine, administration of liberal amounts of fluids, application of epsom salt packs and use of a diet low in protein and fat.^{68c} During the intercritical periods small doses of colchicine are given and a purine-free diet, low in fat and high in carbohydrates, is prescribed. In Central Europe the war has shown that a meatless diet is of value.^{68e}

Fibrositis.—The term fibrositis has long been used to designate a disease characterized by pain and nodules in the muscles and especially by changes in the fibrinous structure. In this country fibrositis has not been designated as such, or possibly has not been recognized.

Moynahan and Nicholson⁶⁹ report 5 typical cases, with a discussion of the incidence, etiology, pathology, symptomatology, differential diagnosis and treatment. They used infiltration with procaine hydrochloride and achieved good results. Schmidt,⁷⁰ on the basis of a study of the miners employed by the Butterley Company, says that fibrositis is the most common rheumatic disease in English coal miners. Because of it not less than 2,465 shifts and 15,958 tons of coal

64. Rosenberg, E. F.: Present Status of Gold Therapy for Rheumatoid Arthritis, Proc. Staff Meet., Mayo Clin. **17**:264-271 (April 29) 1942.

65. Freyberg, R. H.: Gold Salts in the Treatment of Chronic Arthritis: Metabolic and Clinical Studies, Proc. Staff Meet., Mayo Clin. **17**:534-541 (Oct. 21) 1942. Robinson, R. H.: Gold Therapy in Rheumatoid Arthritis, Canad. M. A. J. **47**:158-161 (Aug.) 1942. Preston, W. S.; Block, W. D., and Freyberg, R. H.: Chemotherapy of Chronic Progressive Arthritis of Mice: Role of Sulfur in Gold-Containing Compound, Proc. Soc. Exper. Biol. & Med. **50**:253-256 (June) 1942. Freyberg, Block and Wells.⁶²

66. Snyder, R. G.; Traeger, C. H., and Squires, W. H.: Toxic Reactions and Death Following Gold Therapy in Chronic Arthritis, Indust. Med. **11**:425-429 (Sept.) 1942.

67. Fenz, E.: Ebesal (Copper Preparation) in Chronic and Subacute Arthritis, München. med. Wchnschr. **88**:1101-1105 (Oct. 10) 1941.

68. (a) Smyth, C. J., and Freyberg, R. H.: A Study of the Hereditary Nature of Gout: A Report of Two Families, Ann. Int. Med. **16**:46-56 (Jan.) 1942. (b) Cohen, A.: Gout and the Negro, South. Med. & Surg. **103**:654-655 (Dec.) 1941. (c) Cohen, A.: Gout: The Modern Disease, *ibid.* **98**:637-642 (Dec.) 1936. (d) McEwen, C.: The Use of High Fat and High Purine Diets in the Diagnosis of Gout, J. Mt. Sinai Hosp. **8**:854-862 (Jan.-Feb.) 1942. (e) Symposium on Gout and Gouty Articular Lesions, Med. Klin. **37**:981 (Sept. 26); 1008 (Oct. 3); 1027 (Oct. 10) 1941. (f) Talbott, J. H.: The Treatment of Gout, Bull. New York Acad. Med. **19**:318-328 (May) 1942.

69. Moynahan, E. J., and Nicholson, E. S.: Value of Procaine Infiltration in Diagnosis and Treatment of Fibrositis, Brit. M. J. **1**:65-68 (Jan. 17) 1942.

70. Schmidt, L.: Rheumatism and Industry: Miners' Share, Brit. J. Phys. Med. **5**:145-148 (Sept.-Oct.) 1942.

have been lost a year in the mines of the Butterley Company alone. On the basis of these figures Schmidt estimates that in Great Britain 1,304,029 tons of coal per year is lost. To the loss of production must be added other economic damages, such as lost wages and costs of medical treatment, which are estimated at 6,000,000 pounds. He quotes Buckley, who studied 5,292 rheumatic patients from an industrial area. One thousand five hundred and eighty-three were miners and 50 per cent of them had fibrositis. Schmidt says that drafts and cold are the chief etiologic factors.

Beeson and Scott⁷¹ report 125 cases of a form of myalgia of the neck which may develop into general fibrositis. It occurred in epidemics, and in 40.8 per cent of the cases there were associated infections of the upper respiratory tract. The trapezius, deltoid, rhomboid and scapular muscles were affected. Fifty-five per cent of the patients complained of tenderness. Nodules in the affected muscles, pain on motion and general discomfort were also frequently associated with the disease. Experiments on human subjects indicated that it could be transmitted by blood but not by nasal secretions. Like many of the more familiar communicable diseases, it is a mild, self-limited infection.

Steinberg⁷² used vitamin E (tocopherols) both orally and parenterally, in the treatment of primary fibrositis. Because both primary fibrositis and nutritional muscular dystrophy respond to such treatment, he concludes that primary fibrositis is a nutritional disease associated with deprivation of vitamin E. He uses 300 mg. of mixed tocopherols daily the first week, 150 mg. by mouth daily for the next two weeks and 100 mg. daily for maintenance. He believes, however, that 1 mg. of tocopherols per kilogram of body weight per day would be sufficient for the average person.

Ingham⁷³ reports 12 cases of primary fibrositis treated with vitamin E. His results substantiate Steinberg's conclusion that vitamin E is of value in the treatment of fibrositis. Relief was obtained in three to four weeks with either wheat germ oil in daily doses of 2 to 8 cc. or synthetic vitamin E (alpha tocopherol acetate) in doses of 3 mg. three times a day.

Palindromic Rheumatism.—In June 1941 Hench⁷⁴ in his presidential address before the meeting of the American Rheumatism Association called attention to a "new" oft recurring disease of joints apparently producing no articular residues. He called this "palindromic rheumatism." It is characterized by multiple afebrile attacks of arthritis, peri-arthritis and para-arthritis, with pain, swelling, redness and disability. It occurs in one to many joints, small or large, and is slightly more prevalent among females. The attack appears suddenly and develops rapidly and lasts from a few hours to several days. In spite of the presence of an acute inflammatory polymorphonuclear exudate, there are no constitutional reactions or abnormalities. Laboratory tests reveal no significant residues after numerous attacks. Hench's cases resemble Solis-Cohen's 27 cases of "angioneural arthrosis," which he described in 1911 and 1913, and Kahlmeter's 45 cases of "allergic

71. Beeson, P., and Scott, T. F. M.: Clinical Epidemiological and Experimental Observations on Acute Myalgia of Neck and Shoulder: Its Possible Relation to Certain Cases of Generalized Fibrositis, *Proc. Roy. Soc. Med.* **35**:733-740 (Sept.) 1942.

72. Steinberg, C. L.: The Tocopherols (Vitamin E) in the Treatment of Primary Fibrositis, *J. Bone & Joint Surg.* **24**:411-423 (April) 1942.

73. Ingham, D. W.: Treatment of Fibrositis with Vitamin E, *M. Ann. District of Columbia* **10**:470-471 (Dec.) 1941.

74. Hench, P. S., and Rosenberg, E. F.: Palindromic Rheumatism: A "New," Oft-Recurring Disease of Joints (Arthritis, Peri-Arthritis, Para-Arthritis) Apparently Producing No Articular Residues: Report of Thirty-Four Cases (Its Relationship to "Angioneural Arthrosis," "Allergic Rheumatism" and Rheumatoid Arthritis), *Proc. Staff Meet., Mayo Clin.* **16**:808-815 (Dec. 17) 1941.

rheumatism," reported in 1939. Hench states that there may be 10 to 250 attacks a year, lasting from two to seven days. In 80 per cent of the cases the usual duration of the attacks was a few hours to three days. In 70 per cent the longest attacks lasted two to five days. In 90 per cent of the cases the attacks were usually monarticular, but the pain was severe. He states that the similarities among angioneural arthrosis, allergic rheumatism and palindromic rheumatism are more numerous than the differences. The differences are that 30 per cent of Solis-Cohen's patient's were under 12 years of age, whereas none of Hench's were under 13 and most were adults. In 70 per cent of Solis-Cohen's cases the attacks were polyarticular; in Hench's cases they were usually monarticular. Forty per cent of Solis-Cohen's patients had febrile attacks; Hench's did not. Solis-Cohen's patients were ill for many weeks; Hench's usually recovered in four or five days. Allergic reactions were uncommon in Hench's cases, as compared with Kahlmeter's.

Thompson⁷⁵ reports 2 cases of palindromic rheumatism, and Mazer⁷⁶ reports the case of a 53 year old man who had had recurrent attacks of acute arthritis for thirty years without permanent changes in the joints.

Rhizomelic Spondylitis (Marie-Strümpell).—Freund,⁷⁷ in a report on a case of rhizomelic spondylitis, states that in the intervertebral articulations all gradations from fibrous to osseous ankylosis were encountered. There was slight evidence of chronic inflammation. The articular processes of the vertebrae contained coarse fibrous tissue exhibiting chronic inflammatory changes, but not showing any specific appearance of typical rheumatic lesions. No signs of degenerative change were seen within the intervertebral articulation. The disks showed replacement of the cartilage and nucleus pulposus by invading blood vessels and fibrous tissue. The most striking feature is the formation of osseous bridges between two adjacent vertebral bodies. He concludes that ossification of the ligaments was not responsible for the stiffness in the spine in this case, since it was only in the early stages.

Through his roentgenographic studies Oppenheimer⁷⁸ found that calcification and ossification of the vertebral ligaments are associated with many different vertebral lesions. He states that they are not typical of any particular disease and should not be confused with arthritis. The ligaments calcify or ossify when their tension and mobility are diminished. Ligaments play no active part in the formation of vertebral osteophytes. He states that complete rigidity of the spine may occur in Marie-Strümpell disease in the absence of ossification of the ligaments. That is, it may be the result rather than the cause of immobility. He believes that calcification or ossification of the vertebral ligaments is a secondary reaction. Its presence often indicates the coexistence of a lesion of the vertebral bone or joints.

Bastow⁷⁹ reports 6 cases of ankylosing spondylitis which illustrate the improvement secured even in long-standing disease by use of a plaster shell and complete

75. Thompson, J. L., Jr.: Palindromic Rheumatism: Report of Two Cases, *M. Ann. District of Columbia* **11**:189 (May) 1942.

76. Mazer, M.: Palindromic Rheumatism, *J. A. M. A.* **120**:364-365 (Oct. 3) 1942.

77. Freund, E.: Contribution to Pathogenesis of Spondylitis Ankylopoietica, *Edinburgh M. J.* **49**:91-109 (Feb.) 1942.

78. Oppenheimer, A.: Calcification and Ossification of Vertebral Ligaments (Spondylitis Ossificans Ligamentosa): Roentgen Study of Pathogenesis and Clinical Significance, *Radiology* **38**:160-173 (Feb.) 1942.

79. Bastow, J.: Some Orthopaedic Procedures Employed in Treatment of Arthritis, *Proc. Roy. Soc. Med.* **35**:80-84 (Dec.) 1941.

rest in bed. Gradual correction of kyphosis was achieved by adding thin layers of padding under the dorsolumbar junction and removing them from under the head. Deep-breathing exercises, daily physical therapy and use of a Goldthwaite spinal brace were other adjuncts to treatment.

Herrick and Tyson⁸⁰ bring out a very important point when they state that ankylosing spondylitis is rare.

Probably the majority of cases are undiagnosed. Many are wrongly diagnosed and wrongly treated. Perhaps the greatest error is the subjection of many of the victims of this disease to spinal fusion—a measure as futile as it is severe. . . .

The penchant of ankylosing spondylitis for the male in the third to the fifth decade, the great variability of the symptoms, the lack of definition in localizing and describing the pain, its intermittent character, the peculiar attitudes and movements of the patient, the immobility of the thoracic cage, the slight or absent fever, the stiffness of the spine and the abnormal straightening of its lumbar segment, the roentgenographic findings, the elevated sedimentation rate, the occasional involvement of the smaller joints of the extremities and the rarer event of an endocarditis of the rheumatic type, all are important diagnostically. If the physician is alert to this picture, confusion with other pathologic states is unlikely.

The importance of roentgen treatment of rhizomelic spondylitis was emphasized several years ago by Freyberg. Smyth, Freyberg and Lampe⁸¹ state that this form of treatment, if adequately and promptly carried out, has usually been found to give relief in the early stages of the disease.

Scott,⁸² of England, has given the lead in this form of treatment. Baker⁸³ is enthusiastic about a combined treatment. Hyperextension exercises are given, and a special three point brace is applied to maintain correction. Roentgen therapy is given over either the entire spine or the involved area. "Two hundred kilovolts is used in treating areas of about five by fifteen centimeters; 150 roentgen units are given over one or more areas daily for three to five treatments; if necessary the dosage is repeated after three to six weeks." Pain is relieved and correction is easier. The most satisfactory results have been obtained when the disease was in the early stages, but surprisingly good improvement has been noted in some of the patients with definite deformity and advanced calcification.

[ED. NOTE.—So far the combination of orthopedic and roentgen therapy has given the best results.]

Blair⁸⁴ feels that the pathologic changes in spondylitis "adolescens" are caused primarily by absorption of the cartilage and not by infection and that the beneficial results of the roentgen treatment are brought about by the liberation of sulfur within the body in such a form that it can replenish a sulfur deficiency. He believes that in spondylitis adolescens chondroitin sulfuric acid is absorbed from the cartilage, the ligaments and the bones in and around the sacroiliac joints and spine and that this absorption occurs because of a deficiency of sulfur or the mucoitin or chondroitin sulfuric acids elsewhere in the body. He believes that the iritis associated with spondylitis adolescens is caused by the same metabolic disturbance and possibly may react favorably to the same treatment.

80. Herrick, W. W., and Tyson, T. L.: The Medical Aspect of Ankylosing Spondylitis (Marie-Strümpell), *Ann. Int. Med.* **15**:994-1001 (Dec.) 1941.

81. Smyth, C. J.; Freyberg, R. H., and Lampe, I.: Roentgen Therapy for Rheumatoid Arthritis of the Spine, *J. A. M. A.* **117**:826-831 (Sept. 6) 1941.

82. Scott, S. G.: Spondylitis Adolescens with Associated Pathological Changes in the Sacro-Iliac Joints, *Charterhouse Rheumat. Clin., Orig. Papers* **1**:169-203, 1937.

83. Baker, L. D.: Rhizomelic Spondylitis: Orthopaedic and Roentgen Therapy, *J. Bone & Joint Surg.* **24**:827-830 (Oct.) 1942.

84. Blair, H. C.: Spondylitis Adolescens—Strümpell-Marie Disease: Practical and Theoretical Considerations, *Surg., Gynec. & Obst.* **74**:663-670 (March) 1942.

Gonorrheal Arthritis.—Kersley and King⁸⁵ report a study of the various manifestations of gonorrheal arthritis. They state that the time between infection and the onset of symptoms referable to the joints may be considerable. In 81 per cent of the cases it was longer than ten weeks. The complement fixation test gave positive results in 80 per cent of cases in which the diagnosis was proved and in 60 per cent of those in which it was probable. Positive reactions have been obtained even twenty years after infection. For treatment they recommend doses of sulfonamide compounds sufficient to maintain a concentration of 6 to 10 mg. per hundred cubic centimeters of blood for ten to fourteen days. Fever induced by intravenous injections of typhoid-paratyphoid combined vaccine each containing 10,000,000 or more organisms or by hyperthermy has also proved effective. When hyperthermy is used the temperature is raised to 106 to 107 F. in two to four sessions of 6 to 10 hours each. Ninety per cent of the patients so treated were cured. The combination of sulfanilamide with hyperthermy gives excellent results.

Bauer, Ropes and Short⁸⁶ state that the incidence of permanent disability, which was formerly about 25 per cent, should be greatly reduced if treatment with sulfonamide compounds is given early. They prefer sulfathiazole because it is less toxic and use 2 Gm. as the initial dose.

Vitamin D.—The controversy still goes on about vitamin D.⁸⁷ Snyder, Squires Forster and Traeger⁸⁸ still claim that treatment with vitamin D produces definite functional improvement and that it is safe. Steck⁸⁹ reports:

There is still no adequate explanation of the beneficial results of this method of treating arthritis.

There is no claim that vitamin D is a specific cure for arthritis. Complete freedom from any recurrence of symptoms on cessation of treatment for long periods was found only in a small percentage of cases studied over a period of five years.

However, Slocumb,⁹⁰ states that large doses of vitamin D partially controlled the symptoms of infectious arthritis in 7 of 14 cases. Twenty-five courses of daily doses of 52,500 to 386,000 units were given. The periods of treatment lasted from twelve days to fifteen and one-half months. Little objective effect was noted, and beneficial effects were only transitory. There is some risk of renal damage. Gastrointestinal symptoms are indicative of toxicity.

Warkany, Guest and Grabill⁹¹ state: "After abrupt withdrawal of the high daily doses of vitamin D from three to six months elapsed before the concentration of vitamin D in the blood serum fell to a normal level."

85. Kersley, G. D., and King, A.: Discussion on Gonococcal Arthritis and "Rheumatism," Proc. Roy. Soc. Med. **35**:653-658 (Aug.) 1942.

86. Bauer, W.; Ropes, M. W., and Short, C. L.: The Treatment of the Infectious Arthritides with Sulfonamide Compounds, M. Clin. North America **26**:1529-1550 (Sept.) 1942.

87. Reynolds, C.: Comparative Therapeutic Value and Toxicity of Various Types of Vitamin D, Journal-Lancet **62**:372-375 (Oct.) 1942.

88. Snyder, R. G.; Squires, W. H.; Forster, J. E., and Traeger, C. H.: Treatment of Two Hundred Cases of Chronic Arthritis with Electrically Activated Vaporized Sterol, Indust. Med. **11**:295-316 (July) 1942.

89. Steck, I. E.: Further Clinical Experience in Treatment of Arthritis with Vitamin D, Ohio State M. J. **38**:440-443 (May) 1942.

90. Slocumb, C. H.: Vitamin D in the Treatment of Infectious Arthritis, Ann. Int. Med. **16**:241-245 (Feb.) 1942.

91. Warkany, J.; Guest, G. M., and Grabill, F. J.: Estimation of Vitamin D in Blood Serum: Vitamin D in Human Serum During and After Periods of Ingestion of Large Doses of Vitamin D, J. Lab. & Clin. Med. **27**:557-565 (Jan.) 1942.

Psoriasis.—Bauer, Bennett and Zeller⁹² conclude that “the pathological changes in the joints of patients with arthritis and psoriasis are usually indistinguishable from those of uncomplicated rheumatoid arthritis. . . . Until additional studies have been made, it is our belief that if the term *psoriatic arthritis* is to be used to designate a form of articular disease its use should be restricted to cases in which the arthritis is limited to the terminal phalangeal joints.”

Franks and Wallace⁹³ state that 4 per cent of all cutaneous diseases in America are psoriasis. Arthropathic psoriasis has two forms. The first and more common type follows resistant psoriasis of long duration, while the second type develops simultaneously with the eruption. The rapid improvement in many of the cases of arthritis after the involution of the cutaneous eruption would indicate that the arthritis may be secondary to the disease of the skin. The arthritis was definitely of the atrophic type. Another interesting statement is that the sedimentation rate is usually normal in psoriasis, whereas in arthritis it is rapid. The amount of cholesterol in the blood is high in psoriasis.

Menopausal Arthritis.—Ishmael⁹⁴ discusses the treatment of menopausal arthritis. General supportive measures include a diet poor in carbohydrates and rich in vitamins for overweight patients and a normal well balanced diet for those whose weight is normal. Trauma, cold and dampness are to be avoided. Foci of infection are best left intact while active treatment is in progress. Supplementary vitamins are useful when a chemical deficiency is present. Relief of such associated symptoms as gastrointestinal disturbances, emotional upsets and faulty posture may relieve the pain. Specific measures are of two kinds, injections of natural estrogenic substances and injections of diethylstilbestrol. Eighty per cent of the patients whose disease was diagnosed as menopausal arthralgia had satisfactory remissions after the injection of diethylstilbestrol. “In 30 patients, stilbestrol was successfully substituted for estrin. . . . Twenty-three patients (77 per cent) receiving stilbestrol by mouth had clinical remissions as compared with 10 patients (30 per cent) who received estrin that responded by clinical remissions.”

Infection.—Very little has been written about infection of late. Bassler⁹⁵ states that infections of intestinal origin may be an important factor in the causation of arthritis and suggests a method of biologic and dietetic treatment. The results of gastrointestinal treatment of 205 cases. are presented. About 17 per cent of the patients with digestive diseases causing secondary biotoxic states showed improvement. Among 181 patients with primary biotoxic intestinal conditions, 68.5 per cent showed definite reduction of swelling, with improvement in function of the joints and control of remissions. About 26.5 per cent more were distinctly improved, and for 9.2 per cent the treatment failed.

Preston⁹⁶ like Sabin⁹¹ experimented with the arthritis in rats caused by pleuropneumonia-like micro-organisms in an attempt to isolate similar organisms from

92. Bauer, W.; Bennett, G. A., and Zeller, J. W.: Pathology of Joint Lesions in Patients with Psoriasis and Arthritis, Tr. A. Am. Physicians **56**:349-352, 1941.

93. Franks, A. G., and Wallace, J. J.: Arthropathic Psoriasis, Mil. Surgeon **91**:199-205 (Aug.) 1942.

94. Ishmael, W. K.: Menopause Arthralgia, J. Lab. & Clin. Med. **27**:297-303 (Dec.) 1941; Oral Stilbestrol Therapy in Menopause Arthritis, J. A. M. A. **117**:1650 (Nov. 8) 1941.

95. Bassler, A.: Intestine and Chronic Arthritis, Am. J. M. Sc. **203**:698-708 (May) 1942.

96. Preston, W. S.: Arthritis in Rats Caused by Pleuropneumonia-Like Micro-Organisms and Relationship of Similar Organisms to Human Rheumatism, J. Infect. Dis. **70**:180-184 (March-April) 1942.

patients suffering from rheumatoid arthritis. On no occasion was any organism related to the pleuropneumonia group obtained. These negative results agree with those of all other workers reporting similar studies.

Each year more is written about rheumatism connected with brucellosis. Manchester⁹⁷ concludes after study of 100 cases that the articular symptoms are not associated with residual deformity or permanent impairment of function. There is no relation between brucellosis and rheumatoid arthritis. Phalen and Prickman⁹⁸ report 3 cases of brucellosis spondylitis. The organisms were demonstrated. Fever therapy was effective, although it is not commonly so for other kinds of spondylitis.

Bauer, Ropes and Short⁸⁶ report that sulfanilamide and its derivatives are of value in the treatment of arthritis produced by gonorrhea and infections due to streptococci, the meningococcus, the colon bacillus or the pneumococcus. They are of questionable value in undulant fever and lymphogranuloma venereum. Their value for scarlet fever, bacillary dysentery, typhoid, subacute bacterial endocarditis and chronic idiopathic ulcerative colitis is undetermined. They are ineffectual in rheumatic fever, rheumatoid arthritis, tuberculous arthritis and the articular lesions associated with lupus erythematosus disseminatus.

The advent of the sulfonamide compounds represents the greatest advance ever made in the treatment of joint disease. The dramatic alteration in the clinical course of many of the specific infectious arthritides, following the administration of sulfonamide compounds, is adequate evidence that they exert a specific chemotherapeutic effect on certain causative organisms.

Hypertrophic Arthritis of the Hip.—Harmon⁹⁹ reports the results of treatment of 79 patients with hypertrophic arthritis of the hip. Two thirds of them were given significant relief from pain and disability by conservative treatment. Harmon feels, however, that operation, preferably arthrodesis or arthroplasty, offers the only lasting relief. Kuhns,¹⁰⁰ on the other hand, says that the symptoms are caused by strain on the muscles and ligaments due to faulty posture. One hundred and fifty-eight patients were given orthopedic treatment designed to correct the strain. Forty-seven, or 29.8 per cent, were relieved of symptoms and 58, or 36.7 per cent, showed great improvement.

Psychologic Aspects.—Halliday¹⁰¹ found that with 9 of 20 patients with arthritis the onset of the disease was preceded by emotional upsets due to shock, danger, family worries or fear of loss of a love object, with resultant depression, and feelings of frustration. All of them dealt with emotion in a common way. Their feelings were "bottled up." This restriction of feeling and of emotional expression is considered characteristic of the patient with rheumatoid arthritis. Like peptic ulcer, mucous colitis, exophthalmic goiter and asthma, arthritis has phases of ups and downs which can be associated with emotional variations. Halliday states that apparent cures have been produced by pregnancy or by an attack of jaundice. He feels that study of patients who recover "on their own" is important.

(To Be Continued)

97. Manchester, R. C.: Clinical Manifestations and Diagnosis of Chronic Brucellosis, *Ann. Int. Med.* **16**:950-965 (May) 1942.

98. Phalen, G. S.; Prickman, L. E., and Krusen, F. H.: Brucellosis Spondylitis: Treatment of Physically Induced Hyperpyrexia, *J. A. M. A.* **118**:859-862 (March 14) 1942.

99. Harmon, P. H.: Pathology and Treatment of Osteoarthritis of Hip, with Special Emphasis on Pin Arthrodesis and Cup Arthroplasty, *Pennsylvania M. J.* **45**:948-956 (June) 1942.

100. Kuhns, J. G.: Orthopaedic Treatment of Hypertrophic Arthritis of the Hip, *J. Bone & Joint Surg.* **24**:547-554 (July) 1942.

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A CAUTION AGAINST TOO LIBERAL USE OF CITRATED BLOOD IN TRANSFUSIONS

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The use of citrated blood for transfusion has become so common in the last twenty-five years that it would seem to be entirely safe if ordinary precautions are taken to resort to compatible blood and to avoid the presence of pyrogens. Nevertheless, some experiences which we have had have caused us to question the innocuousness of sodium citrate itself, when injected in large quantity. The possibility of an overdosage of sodium citrate was especially suggested by the unexplained death of a patient who received 4,000 cc. of citrated blood in six hours after a revision thoracoplasty.

The toxicity of sodium citrate was well known when Lewisohn¹ introduced transfusion of citrated blood in 1915; its presence was blamed for the fact that the number of reactions associated with this method was greater than that associated with other methods (Unger,² Bernheim³). Drinker and Brittingham⁴ and Unger⁵ advanced some evidence showing that sodium citrate increased the fragility of the red blood cells, that it decreased the available quantity of complement and that it reduced the phagocytic power of the white blood cells and the function of the opsonins. However, these conclusions were not substantiated by the work of Mellon, Hastings and Casey⁶ and Gichner.⁷ Other factors have now been shown to be the cause of most transfusion reactions following the administration of citrated blood. The elimination of pyrogenic substances established by Seibert⁸ and the improvements in the care of the apparatus stressed by Lewisohn and

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1. Lewisohn, R.: A New and Greatly Simplified Method of Blood Transfusion, *M. Rec.* **87**:141, 1915.

2. Unger, L. J.: The Therapeutic Aspect of Blood Transfusion, *J. A. M. A.* **73**:815 (Sept. 13) 1919.

3. Bernheim, B. M.: Whole Blood Transfusion and Citrated Blood Transfusion, *J. A. M. A.* **77**:275 (July 23) 1921.

4. Drinker, C. K., and Brittingham, H. H.: The Cause of Reactions Following Transfusion of Citrated Blood, *Arch. Int. Med.* **23**:133 (Feb.) 1919.

5. Unger, L. G.: The Deleterious Effects of Sodium Citrate Employed in Blood Transfusions, *J. A. M. A.* **77**:2107 (Dec. 31) 1921.

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7. Gichner, M. G.: Studies of Citrated Blood: Behavior of Platelets, *J. A. M. A.* **88**:893 (March 19) 1927.

8. Seibert, F. B.: Fever-Producing Substances Found in Some Distilled Waters, *Am. J. Physiol.* **67**:90, 1923.

Rosenthal⁹ have so reduced reactions following transfusions of citrated blood that their incidence is now no greater than when the blood is prepared by other methods (Lewisohn,¹⁰ Zimmerman¹¹).

From the very first, however, it was realized that too large amounts of sodium citrate could prove harmful. After experiments on dogs, Lewisohn¹² concluded that 15 Gm. would be a fatal dose for a man weighing 125 pounds (56.7 Kg.). He advised that 5 Gm. be the maximum dose used in transfusions. No mention was made, however, of the time over which such an amount could be given. Salant and Wise¹³ in 1916 showed that for experimental animals the toxicity of sodium citrate depended on the rate of injection. This fact was demonstrated in human beings by Krautwald and Dorow.¹⁴ They observed that tetany appeared in human subjects following the rapid introduction of 5 Gm. of sodium citrate intravenously (i. e., in a few minutes) and that the rapidity of onset and the severity of symptoms varied with the dose and the rate of administration.

Since Lewisohn's pioneering work in 1915, the dosage limit set by him often has been exceeded. Marriott and Kekwick¹⁵ reported giving as much as 5,600 cc. of citrated blood over a period of forty-eight hours. It is to be noted that all the reported massive transfusions were given slowly, i. e., over a relatively long period. In recent years, however, broadening of the indications and scope of major surgical procedures and better understanding of the advantages of transfusions in cases of shock and hemorrhage have led to a more frequent and quantitatively greater use of blood as well as to its more rapid injection. This work was undertaken in an effort to determine the effects of the introduction of large quantities of citrated blood in a short period.

EXPERIMENTAL PROCEDURE

The experimental procedure consisted of bleeding unanesthetized dogs 1 per cent of their body weight at half-hourly intervals. The blood obtained, after being mixed with an anticoagulant, was reinjected intravenously. Mongrel dogs were used, and with a few exceptions they were kept only a few days before being submitted to the experimental procedure. All were made to fast for eighteen hours previous to the experiment. The bleeding was carried out through a cannula introduced into the femoral artery. The blood was injected by means of an ordinary transfusion set into the femoral vein on the opposite side. The rate of flow was regulated so that the transfusion was almost completed in thirty minutes. Blood pressure readings were obtained with a mercury manometer before each bleeding. At regular intervals, samples of venous blood were obtained from the site of injection for determination of hematocrit values, clotting time and calcium and phosphorus content. This procedure was carried out on two groups of dogs. In group A (8 dogs) sodium citrate was used as an anticoagulant. Enough of a 5 per cent solution was mixed with the blood to obtain a final concentration of 0.6 per cent sodium citrate. In group B (8 dogs) heparin¹⁶ was used as a control, 0.085 cc. of heparin diluted in 5 cc. of saline solution being added to each 100 cc. of blood. Between 10 and 20 cc. of blood was lost through different causes at each bleeding.

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10. Lewisohn, R.: Twenty Years' Experience with the Citrated Method of Blood Transfusion, *Ann. Surg.* **105**:602, 1937.

11. Zimmerman, L. M.; Strauss, A. M., and Laufman, H.: Blood Transfusion Reactions: Their Causes and Prevention, *Ann. Surg.* **114**:961, 1941.

12. Lewisohn, R.: Blood Transfusion by the Citrated Method, *Surg., Gynec. & Obst.* **21**:37, 1915.

13. Salant, W., and Wise, L. E.: The Action of Sodium Citrate and Its Decomposition in the Body, *J. Biol. Chem.* **28**:27, 1916.

14. Krautwald, A., and Dorow, H.: Ueber die Verträglichkeit grösserer intravenöser Natriumcitratgaben, *Arch. f. exper. Path. u. Pharmakol.* **194**:691, 1940.

15. Marriott, H. L., and Kekwick, A.: Continuous Drip Blood Transfusion, *Lancet* **1**:977, 1935.

16. From the Lederle Laboratories, Inc., Pearl River, N. Y.

EXPERIMENTAL RESULTS

For dogs in group A, in which replacement was effected with citrated blood, the average survival period was slightly over four and one-half hours (chart 1). These animals withstood an average of nine and twenty-five hundredths bleedings before death. In 5 of these dogs, dyspnea, convulsions or fibrillary twitchings were observed prior to death. In 3 dogs dyspnea alone was noted. Individual variations were not outstanding in this group of animals. For group B the average survival period was almost three times as long, i. e., over twelve

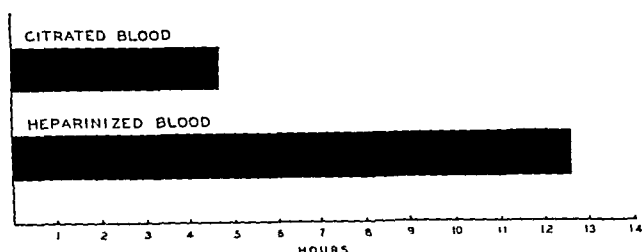


Chart 1.—Survival of dogs receiving heparinized blood and those receiving citrated blood.

TABLE 1.—Serum Calcium Values for Four of the Dogs Given Transfusions of Citrated Blood

Number of Dog	Serum Calcium, Mg. per 100 Cc.	
	Initial (Before Experiment)	Terminal (Before Death)
12.....	10.7	16.5
15.....	12.6	15.4
19.....	8.5	10.5
30.....	10.0	13.3

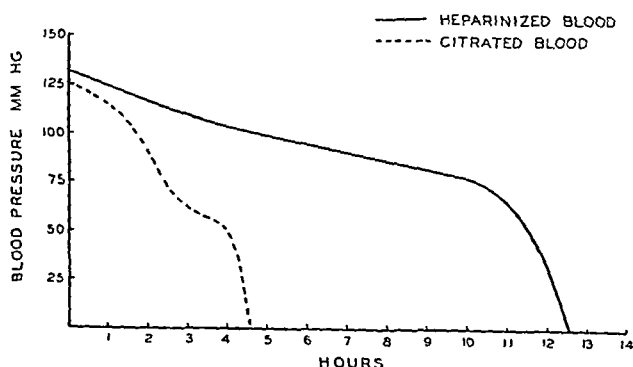


Chart 2.—Average blood pressure curves observed in the animals given transfusions of heparinized blood and those given transfusions of citrated blood.

and one-half hours, corresponding to an average of 25.2 bleedings (table 1). In no instance were convulsions and fibrillary twitchings noted. The individual variations in this group were greater than in group A.

In group A the blood pressure was observed to drop to a relatively low level even two and one-half hours before death. No similar drop was noted in the animals receiving heparinized blood (group B) (chart 2).

In both groups the hematocrit values were comparable and changed little during the course of the experiment. The average drop in the reading was 4 points. One animal in each group, however, had a rise of 5 points.

In group A, during the first hour, the clotting time, as determined by the Howell method, showed a slight but constant decrease, averaging two and eight-tenths minutes. Shortly before the death of 3 dogs in this group the clotting time had increased by about ten minutes, but the other 5 animals showed no significant changes. In group B, the clotting time did not show any initial decline and in all animals it was greatly lengthened toward the end of the experiment, the maximum increase being seventy-two minutes.

The serum calcium values determined for 4 dogs given transfusions of citrated blood showed a definite increase prior to death (table 1). There were no significant changes in the initial and terminal serum calcium values of 7 of the dogs given transfusions of heparinized blood (table 2). Unfortunately, reliable determinations of serum phosphorus could not be made in many instances, because some specimens had to stand several hours before being analyzed.

COMMENT

The animals given transfusions of heparinized blood survived, on the average, almost three times as long as those given transfusions of citrated blood. Moreover, the latter showed before death definite toxic symptoms not seen in the

TABLE 2.—*Serum Calcium Values for Seven of the Dogs Given Transfusions of Heparinized Blood*

Number of Dog	Serum Calcium, Mg. per 100 Cc.	
	Initial (Before Experiment)	Terminal (Before Death)
29.....	10.5	9.9
13.....	10.9	10.5
14.....	8.3	8.4
28.....	10.0	10.3
35.....	10.4	9.7
36.....	10.3	10.9
38.....	12.2	11.8

former. These differences indicate that citrated blood given in very large amounts over a short period is inferior as a means of replacement to heparinized blood and may even be harmful, owing undoubtedly to the rapid introduction of large amounts of sodium citrate.

A comparison of the blood pressure curves for the two groups suggests that citrated blood will not maintain the blood pressure as well as heparinized blood. This may possibly be due to a toxic effect of sodium citrate manifesting itself even two hours before lethal conditions are attained. Love¹⁷ has shown previously that injection of 35 mg. of sodium citrate per kilogram of body weight depresses the action of the heart muscle. In view of the wide variation present in biologic experiments of this kind, we feel that the evidence is not sufficiently strong to be more than suggestive of this conclusion.

The paradoxical shortening of the clotting time observed early after the administration of citrated blood corroborates the findings of Lewisohn.¹ This effect was at one time advocated by Neuhoof and Hirschfeld¹⁸ as a therapeutic measure for internal hemorrhage. This phenomenon has been attributed to injuries

17. Love, G. R.: Studies on the Pharmacology of Sodium Citrate: I. Circulation, *J. Lab. & Clin. Med.* 9:175, 1923.

18. Neuhoof, H., and Hirschfeld, S.: Slow Intravenous Administration of Large Doses of Sodium Citrate: New Method of Control of Bleeding, *New York M. J.* 113:95, 1921.

to the platelets, but no satisfactory explanation exists at this time. On the other hand, the lengthening of the clotting time observed after massive transfusions with heparinized blood was so great as to militate against the use of this method in other than small routine transfusions. This was true even though the amount of heparin used in the present experiments was too small to prevent clotting entirely. A large needle had to be used, and even this would not prevent the flow of blood from being slowed or even stopped by clotting. This is in accordance with the previous observations reported by Sappington.¹⁹

Sodium citrate forms with calcium a complex soluble salt which liberates very few calcium ions. The characteristics of this substance have been established by a study of its chemical behavior (Sabbatani²⁰), by conductivity measurements (Shear and Kramer²¹) and by its pharmacologic action (Hastings and McLean²²). It is generally held that it is the formation of this salt which prevents the clotting of blood in vitro by removing the calcium ions necessary for coagulation. The tetany observed in animals and man following the intravenous administration of sodium citrate is attributed to the same phenomenon. Death also probably can result from this cause. Whether the death of our animals was due to this action of sodium citrate must remain unanswered until a more practical method of determining the ionized calcium in the blood becomes available.

Actually, there is a great variation in the reported effects of sodium citrate on the total calcium content of the blood. Tsai and Hsu²³ showed that its intravenous injection resulted in a slightly decreased plasma calcium which reverted to normal in twenty-four hours. By the slow intravenous injection of a 1.5 per cent solution of sodium citrate, we were able to confirm these results in contrast to the increase in total calcium observed in our experiments in which repeated transfusions of citrated blood were given. Shohl²⁴ and Krautwald and Dorow¹⁴ have stated that the total calcium level does not change as a result of administration of citrate. Hastings²⁵ seems to have agreed with the authors just mentioned; in addition, he showed that if excretion and oxidation are prevented by tying off the kidneys and liver calcium is drawn from the body stores and the total calcium of the blood is increased. Using the microincineration technic, Scott and Lansing²⁶ have demonstrated that administering sodium citrate to cats by perfusion will lead to depletion of the body cells in calcium and magnesium. At present, however, it

19. Sappington, S. W.: The Use of Heparin in Blood Transfusion, *J. A. M. A.* **113**:22 (July 1) 1939.

20. Sabbatani, L.: Calcium et citrate trisodique, *Arch. ital. de biol.* **36**:397, 1901.

21. Shear, M. J., and Kramer, B.: Composition of Bone: Some Properties of Calcium Citrate, *J. Biol. Chem.* **79**:161, 1928.

22. Hastings, A. B.; McLean, F. C.; Eichelberger, L.; Hall, J. L., and Da Costa, E.: The Ionization of Calcium, Magnesium and Strontium Citrates, *J. Biol. Chem.* **107**:351, 1934.

23. Tsai, C., and Hsu, F. Y.: Effect of the Intravenous Injection of Sodium Citrate and Oxalate on the Concentration of Plasma Calcium and Inorganic Phosphorus, *Chinese J. Physiol.* **4**:273, 1930.

24. Shohl, A. T.: *Mineral Metabolism*, New York, Reinhold Publishing Corporation, 1939, p. 137.

25. Hastings, A. B., cited by Shohl.²⁴

26. Lansing, A. I., and Scott, G. H.: The Effects of Perfusion with Sodium Citrate on the Content and Distribution of the Minerals of Various Cells of the Cat as Shown by Electron Microscopy and Microincineration, *Anat. Rec.* **84**:91, 1942.

is only on hypothetic and questionable grounds that one would suggest that the increases in total serum calcium observed in the present experiments are due to a withdrawal of calcium from the tissues and are an expression of an alteration of the degree of calcium ionization in the circulating blood.

The presence of sodium citrate appears to be responsible for the earlier death of the dogs in group A, but it may not be the only factor. For example, we have given other dogs equivalent amounts of sodium citrate over a similar period of time. None of these experiments resulted fatally. This would seem to indicate that a lethal amount of sodium citrate was not attained in the experiments which have been reported. The ultimate death of the dogs given transfusions of heparinized blood shows that the repeated insults inflicted on the organism during our experiments produce in themselves deleterious effects. Whether these conditions will lead to decreased tolerance to sodium citrate is not known. But the findings of Hastings would indicate that the lowering of the blood pressure observed in these experiments might decrease the tolerance of the organism by rendering renal elimination and hepatic oxidation less effective.

However, under these experimental conditions it seems that the earlier deaths of the animals in group A should be ascribed to the presence and effects of excessive amounts of sodium citrate, although very little light can be thrown on the mechanism of this action.

The clinical application of these experimental findings is difficult. There is no evidence at hand as to the exact rate of oxidation and elimination of sodium citrate in human beings. Since its toxic effects have been shown to vary with the dosage and repetition of a certain dose, with the rate of administration, with different animal species and even with individual members of the species, the safe amount to be injected under given conditions cannot easily be determined. To duplicate our experimental conditions, a man weighing 70 Kg. would have to be given 6,300 cc. of blood containing 0.6 per cent citrate within a few hours. The concentration of 0.6 per cent used in these experiments is higher than that in general use. Since the advent of blood banks, however, concentrations often have been increased up to 0.5 per cent and even higher. Patients requiring the rapid administration of such large amounts of blood are usually desperately ill. Whether their condition decreases their tolerance to sodium citrate is not yet known. All these factors make it impossible to establish the safe amount of citrated blood to be given in a certain period. Quantities of 2,000 or even 3,000 cc. in a few hours have been given without apparent ill effects. From our experimental evidence we feel that a warning should be given against the too liberal use of citrated blood. When extreme conditions prevail and such amounts have been given within a few hours, it would seem advisable to resort to other methods if blood must still be given.

SUMMARY

Dogs bled repeatedly and continually given transfusions of citrated blood survived a much shorter time than controls receiving heparinized blood.

This difference seems to be due to the toxic action of large amounts of sodium citrate. The possible mechanism of its action is discussed on purely theoretic grounds.

The clinical implication of these findings is a warning against the too liberal use of large amounts of citrated blood over a very short time.²⁷

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27. After this work was practically completed, we saw the important article of A. C. Ivy, H. Greengard, I. F. Stein, F. S. Grodins and D. F. Dutton (The Effects of Various Blood Substitutes in Resuscitation After an Otherwise Fatal Hemorrhage, Surg., Gynec. & Obst. **76**:85, 1943). Their results with citrated plasma and citrated blood were definitely inferior to those obtained with heparinized plasma, as determined by survival rates in experimental animals following a single massive hemorrhage. It is noteworthy that our experiments, performed in a somewhat different manner, likewise demonstrated the undesirability of large amounts of citrated blood.

EFFECTS OF MORPHINE IN EXPERIMENTAL SHOCK DUE TO HEMORRHAGE

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The following statements regarding the use of morphine in the treatment of injured patients were made by Cannon¹ in 1923:

Concerning the use of morphine there have been differences of opinion. It has been given to badly wounded men hypodermically even in as large a dose as one grain [0.06 Gm.]. Crile and Lower have advocated giving the drug to the point at which respiration sinks to at least 12 per minute. On the other hand Marshall, who has had very large experience in anesthetizing shocked men, has testified that the severely wounded, when deeply morphinized, make an unsatisfactory recovery after operation. . . . As experiments have proved, after morphine the blood pressure may be lowered further without producing acidosis than is possible otherwise, an observation which suggests that morphine lessens metabolism at a time when the oxygen, needed for the maintenance of chemical changes in the cells, is likely to be insufficient. The drug should be given therefore until the patient is comfortable and quiet. In some cases $\frac{1}{4}$ grain [0.015 Gm.] may be sufficient, in others $\frac{1}{2}$ grain [0.03 Gm.] may be needed. The dose should be repeated if necessary.

It is generally agreed at the present time that the use of morphine is indicated in the treatment of the majority of patients with severe injuries, exceptions including those with intracranial damage. There is, however, a difference of opinion as to the dose. Some are of the opinion that the routine dose for an injured adult should be $\frac{1}{2}$ grain (0.03 Gm.) hypodermically, whereas others maintain that this amount is dangerous and that a single injection should not exceed $\frac{1}{4}$ grain (0.015 Gm.), to be repeated if necessary. Dogmatism regarding the dosage appears to be necessary because the nature of present warfare is such that a physician is not always at hand, and the drug in proper form and dose should be available for administration by the injured person or by an associate.

Large doses of morphine usually cause nausea and vomiting and often diarrhea when administered to dogs. Such effects are observed less frequently in man, but they do occur. Since with dogs large amounts of morphine cause the loss of fluid from the body in the vomitus and stools, the question arises as to whether the drug decreases tolerance to bleeding. Hemorrhage was chosen as the method for causing peripheral circulatory failure, because it is probably the most common cause of shock in injured human beings and because the effects can be studied experimentally without the necessity for producing deep narcosis.

METHODS AND RESULTS

Large animals were used in all experiments. They were given no food but were allowed water during the eighteen hours preceding the determination of the blood volume. The dye-dilution method (T-1824) as revised by Price and Longmire² was used for determinations of plasma volume, and the blood volume was calculated after the hematocrit reading had been

From the Department of Surgery of the Johns Hopkins University and Hospital. The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Johns Hopkins University.

1. Cannon, W. B.: *Traumatic Shock*, New York, D. Appleton and Company, 1923.

2. Price, P. B., and Longmire, W. P.: *The Use of T-1824 in Plasma Volume Determinations*, Bull. Johns Hopkins Hosp. 71:51, 1942.

determined on arterial blood by the use of Wintrobe tubes. The experiment proper was performed twenty-four hours after the studies on blood volume. A total of 20 experiments was performed. Ten of the animals were given hypodermically 1 mg. of morphine sulfate per kilogram of body weight. All of these animals vomited, and 3 of the 10 had loose bowel movements. The morphine was given thirty minutes before the beginning of the experiment. No anesthetic agent was used for the remaining 10 animals except for the injection of procaine hydrochloride at the site at which a cannula was placed in the femoral artery.

The removal of blood from the femoral artery was carried out as follows: At the beginning of the experiment, blood equal to 10 per cent of the calculated blood volume was withdrawn and the animal was removed from the table. This procedure was repeated one hour and two hours subsequently. Thereafter, blood equal to 2.5 per cent of the original blood volume was removed at fifteen minute intervals until death ensued. The experiments were performed in pairs, one animal having had morphine and the other not having had it, and an attempt was made to use dogs of essentially the same weight and build.

The Effects of Morphine on the Bleeding Volume

Narcotic	Experiment No.	Body Weight, Kg.	Plasma Volume, Cc.	Hematocrit Reading	Whole Blood Volume, Cc.	Total Quantity of Blood Removed		Hematocrit Reading	
						Per Cent Blood Volume	Per Cent Body Weight	Control	Terminal
Morphine sulfate	1	13.7	690	49.8	1,360	61.2	5.8	43.7	30.0
	3	13.1	609	55.2	1,333	47.5	4.8	50.4	43.5
	5	12.5	841	43.5	1,478	60.0	7.1	42.0	22.3
	7	11.4	699	52.0	1,458	57.5	7.3	49.4	39.6
	9	15.8	749	55.1	1,652	50.0	5.2	55.4	56.2
	11	12.8	700	50.6	1,460	50.0	5.7	49.6	52.2
	13	11.5	701	33.0	1,129	52.5	5.3	43.3	36.8
	15	9.7	462	51.2	877	57.5	5.2	45.0	37.2
	17	11.0	588	35.0	842	47.5	3.6	36.5	35.3
	19	11.7	517	49.8	1,036	45.0	4.0	46.7	40.4
None	2	14.0	536	52.1	1,120	60.0	4.8	49.0	35.4
	4	12.2	755	47.1	1,378	45.0	5.1	46.8	42.2
	6	12.4	743	47.0	1,390	65.0	7.3	43.2	28.4
	8	11.8	645	50.0	1,255	47.5	5.1	51.3	47.3
	10	15.0	712	48.8	1,400	45.0	4.2	44.4	44.7
	12	14.4	890	38.8	1,460	47.5	4.7	38.6	31.4
	14	12.5	792	48.5	1,540	50.0	6.1	50.0	48.3
	16	8.4	622	33.4	935	52.5	5.8	34.5	23.5
	18	13.9	927	33.8	1,380	50.0	5.0	35.0	41.4
	20	16.0	1,098	34.3	1,673	55.0	5.8	36.0	26.5

The calculated control whole blood volumes in the 20 experiments varied from 7.65 to 12.75 per cent of the body weight, the average being 10.26 per cent. The loss of blood which resulted fatally for the morphinized dogs varied from 45 to 61 per cent of the total blood volume, the average being 52.98 per cent. Values for the control (nonmorphinized) animals were almost identical and ranged from 45 to 65 per cent, the average being 51.75 per cent of the total blood volume.

After the systolic arterial blood pressure had been reduced to approximately 70 mm of mercury by the removal of blood in the various experiments, the average quantity of blood which it was found necessary to remove in order to cause death in the control experiments was 88.3 per cent of the calculated whole blood volume. The corresponding figure for the animals given morphine was 10.4 per cent. This difference may be accounted for by the fact that the control arterial pressures were slightly higher in the nonmorphinized animals.

If one ignores the figures for plasma and whole blood volume and calculates the bleeding volume in terms of percentages of body weight, one finds again that there is little difference in the two groups of experiments. The total quantity of blood that was removed from the morphinized animals varied from 3.64 to 7.30 per cent of the body weight, the average being 5.41 per cent. The bleeding volume of the controls ranged from 4.8 to 7.28 per cent of the body weight, the average being 5.38 per cent. All of the results are given in the table.

COMMENT

Since hemorrhage is probably the most frequent cause of shock in warfare, these experiments were performed in order to try to determine the influence of rather large doses of morphine on the tolerance to bleeding. The dose for a man weighing 70 Kg. corresponding to that used in the experiments would amount to slightly more than 1 grain (0.06 Gm.) of morphine sulfate. Despite the loss of fluid from the intestinal tract which followed the injection of the morphine, the quantity of blood that it was necessary to remove in order to cause death was practically identical with that removed from the controls. It must be emphasized, however, that these experiments were of rather short duration and that morphine may lessen patients' chances of recovery from hemorrhage by causing nausea and interfering with the taking of fluids by mouth.

There is no assurance that these results are applicable to human beings. If they are, they indicate that the chances of withstanding severe hemorrhage are not lessened by the administration of rather large doses of morphine.

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ARTERIAL BLOOD SUPPLY OF THE BREAST

REVISED ANATOMIC DATA RELATING TO RECONSTRUCTIVE SURGERY

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The literature on surgical reconstruction of the breast is surprisingly lacking in adequate descriptions of the blood supply. Many of the procedures in common use appear to have been developed without regard for the preservation of vascularization.¹ Still others are based on a concept of the blood supply which more recent studies prove to be erroneous. Yet preservation of the arterial blood supply is one of the most essential factors in the success of mammaplasty.

The breast is a highly vascular organ. Its surgical reconstruction requires wide undermining of skin flaps, excision of large masses of fat and glandular tissue, with rotation and fixation of the remaining parts. In the course of the operation a number of vessels are likely to become severed or twisted, with resultant interference with vascularization. When there is accurate knowledge of the vascular anatomy this contingency can be avoided.² The following factors are of major interest to the surgeon in this connection:

1. Main types and variations in vascularization of the breast.
2. Relationship of the arteries and their branches to the most vulnerable parts of the breast, namely, the areola and the nipple. (This discussion is limited to the arteries, since the veins usually follow the same course.)
3. The depth at which the main vessels and their ramifications are situated with regard to the cutaneous covering and to the gland proper.
4. Symmetry of the vascularization of the breasts.

HISTORICAL DATA

From the point of view of blood supply, the mammary gland can be considered a well nourished organ of the skin. Its developmental history justifies inclusion of the arteries of the breast among the cutaneous arteries.

In 1889, Manchot described the vascularization of the breast in a monograph entitled "Cutaneous Arteries of the Human Body," which was long considered a classic exposition of the subject.³ According to him the main sources of blood supply are (1) the internal mammary artery, (2) the thoracic lateral artery and (3) the third to the seventh intercostal artery (from the aorta). The main blood supply of the breast, according to Manchot, is provided by six or seven branches of the internal mammary artery, the principal one passing through the second intercostal space. The nipple receives its blood supply only from the internal

Read in part before the American Society of Plastic and Reconstructive Surgery.

1. Maliniac, J. W.: The Pendulous Hypertrophic Breast: Comparative Values of Present-Day Methods of Repair and the Procedure of Choice, *Arch. Surg.* **31**:587 (Oct.) 1935.

2. Maliniac, J. W.: Prevention of Necrosis in Plastic Repair of the Breast, *Am. J. Surg.* **26**:292, 1934.

3. Manchot, C.: *Die Hautarterien des menschlichen Körpers*, Leipzig, F. C. W. Vogel, 1889.

mammary artery and the intercostal arteries. Participation of the thoracic lateral artery in the supply of the mammary gland and the nipple is minimized as to the former and denied as to the latter (fig. 1).

In spite of the thoroughness of Manchot's anatomic descriptions, his conclusions were faulty. Anatomic dissection alone was insufficient to reveal the smaller

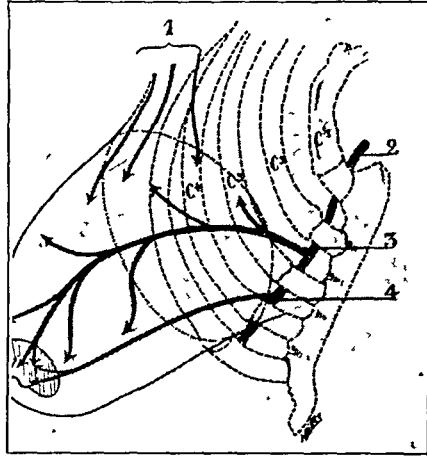


Fig. 1.—Diagrammatic representation of the blood supply of the right breast (Kaufmann). This diagram, although frequently reproduced in textbooks, has been definitely proved inaccurate 1, cutaneous branches originating from the axillary artery, which supposedly do not participate in the blood supply of the gland proper; 2, internal mammary artery; 3, the main perforating artery supplying the gland and nipple; 4, secondary perforating artery of the gland C¹, C², C³ and C⁴ are the respective ribs For comparison, see figures 7 and 10

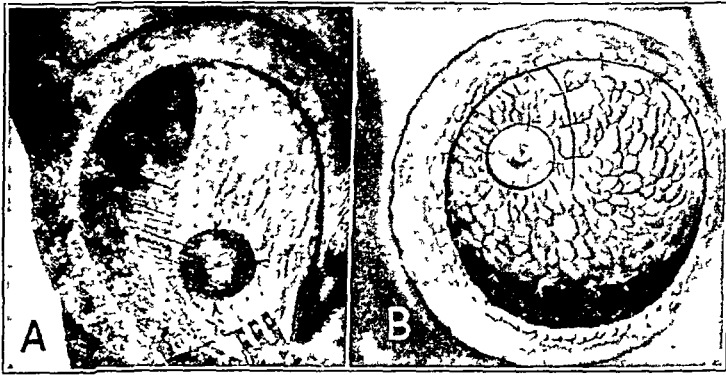


Fig. 2.—Mammoplasty by Biesenberger¹⁴: A, resection of external half of the breast by this procedure totally eliminates the thoracic lateral artery from the blood supply of the remaining gland. In instances in which the thoracic lateral artery is the predominant artery (fig. 7 B) and in cases of radial distribution of the periareolar plexus (fig. 10 C), the nipple will be deprived of adequate blood supply and necrosis is likely to result. B, in addition, upward rotation of the lower pole of the remaining gland is liable to cause torsion of the remaining vessels and thus further interfere with the blood supply.

ramifications observed by later investigators in roentgenograms of injected vessels. In the meantime, however, a number of anatomists accepted and perpetuated Manchot's description of the vascularization of the breast.

Thus, Rauber⁴ stated that the blood supply is provided by the internal mammary artery and the intercostal arteries. Spalteholz⁵ and later Kaufmann⁶ also maintained that the thoracic lateral artery supplies only the cutaneous blood vessels of the breast. On the other hand, Testut⁷ described the thoracic lateral artery as participating in the blood supply of both the gland and the nipple.

Insufficient knowledge of the blood supply had important surgical consequences. Particular attention is directed to a paper by Kaufmann,⁶ which was responsible for the highly questionable procedures of resection of the external half of the breast. This was performed on the assumption that the thoracic lateral artery did not participate in the vascularization of the mamilla and could therefore be sacrificed without danger of necrosis (fig. 2).

Kaufmann's report, presented before the Anatomical Society of Paris in 1933, was severely criticized by Rouvière,⁸ professor of anatomy at the University of Paris. The latter declared, on the basis of the recognized distribution of the lymphatics in this area and the fact that the blood vessels and lymphatics usually follow approximately the same route, that the thoracic lateral artery participates largely in the blood supply of the mammary gland, and in that of the nipple.

As will be shown later, the observations of subsequent investigators confirm Rouvière's statement.

METHODS OF INVESTIGATION

According to some anatomists, an accurate study of the mammary arteries requires the procurement of material from youthful subjects, because after the menopause the breasts become atrophic and the vessels diminish considerably in volume and are not easily penetrated by the injected material. The younger female cadaver, however, is not easily obtainable for study. This may explain some of the contradictory interpretations by different workers. Faulty injections of the vascular system are another cause of erroneous conclusions. In order to obtain accurate data, it is necessary to approach the normal mechanical condition of the living subject and inject the contrast medium into the cadaver through the left carotid artery. Certain of Kaufmann's roentgenograms show that some of the arteries were incompletely filled (fig. 3).

Salmon⁹ carried out his work on 14 adult female breasts. He employed dissection and injection of a contrast medium into the cadaver through the left carotid artery.¹⁰ Two types of roentgenologic studies were made, one of the breast with its cutaneous covering and the other of the breast deprived of the skin. Differentiation between the arterial blood supply of the gland proper and the extraglandular vascularization was thus made possible.

Gitis and Livshits¹¹ based their conclusions on the study of injected blood vessels in 46 female breasts.¹²

4. Rauber, A. A.: *Lehrbuch der Anatomie des Menschen*, ed. 14, Leipzig, Georg Thieme, 1932-1938.

5. Spalteholz, W.: *Handatlas der Anatomie des Menschen*, ed. 12, Leipzig, S. Hirzel, 1937.

6. Kaufmann, R.: *Artères de la glande mammaire chez la femme*, *Ann. d'anat. path.* 10:925, 1933.

7. Testut, J. L.: *Traité d'anatomie humaine*, ed. 8, Paris, Gaston Doin, 1928-1931.

8. Rouvière, in discussion on Kaufmann.⁶

9. Salmon, M.: *Les artères de la peau*, Paris, Masson & Cie, 1936, p. 137.

10. The following material was used for injection: linseed oil, 600 Gm.; powdered colophane, 1,000 Gm.; crystallized phenol, 500 Gm.; lead tetroxide, 2,500 Gm.; ether, 500 Gm.

11. Gitis, M. K., and Livshits, D. L.: *Arterial Supply of the Female Breast*, *Sovet. khir.*, 1936, no. 6, p. 981.

12. The materials for injection were: (1) a suspension of lead tetroxide, liquid petrolatum and turpentine oil, (2) a suspension of official (Russian) mercurial ointment in turpentine oil and (3) a mixture of lead tetroxide in celloidin.

In addition to roentgenographic studies, all investigators used anatomic dissection. The most comprehensive research along this line was done by Marcus,¹³ who examined 53 breasts removed together with the underlying muscular and bony tissue of the chest. He injected the arteries with Teichmann's mixture and left strips of skin along the blood vessels to determine their depth. His procedure was as follows: Vertical and horizontal lines were drawn from the sternoclavicular joint, and both lines were subdivided into centimeters, a coordinating system being established in which the contour of the areola and nipple as well as the course of the vessels was outlined. For practical use, a coordinating chart was drawn on a cellophane sheet which was attached to the mammary gland. Following a thorough study of the surface, a sagittal section of the breast was made in order to ascertain the presence of perforating branches (fig. 4).

As a result of these experimental studies, based on examination of 113 breasts, certain definite data on the vascularization of the breast became available, with



Fig. 3.—Roentgenogram of the injected vessels of the breast which served as basis for the diagram in figure 1. The lack of anastomotic branches between the two main vascular pedicles and around the areola is due to faulty injection technic. (From Kaufmann.⁶)

only minor variations cited by different investigators. These data will be considered in relation to the factors previously cited as of special interest to the surgeon.

COMMON TYPES OF, AND VARIATIONS IN, VASCULARIZATION OF THE BREAST

The blood supply of the breast is extremely abundant and is provided by three main sources: (1) the internal mammary artery, deriving from the subclavian artery (figs. 5 and 6); (2) the thoracic lateral artery, originating from the axillary artery (fig. 7); (3) the intercostal arteries (aorta), of secondary importance (figs. 4 and 8).

13. Marcus, G. H.: *Untersuchungen uber die arterielle Blutversorgung der Mamilla*, Arch. f. klin. Chir. 179:361, 1934.

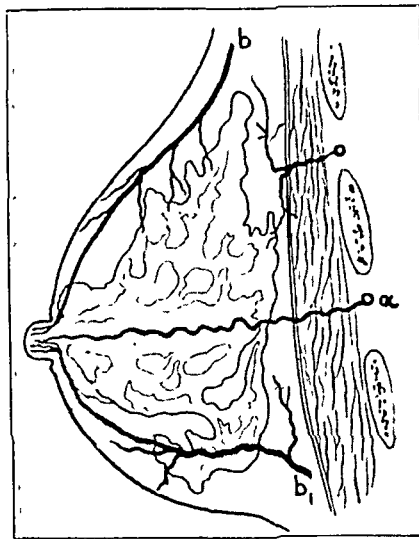


Fig. 4.—Diagram showing the depth of the arteries: *a*, perforating branch of the internal mammary artery penetrating through the entire thickness of the gland to terminate in the nipple; *b* and *b*₁, ramifications of the main arteries, located at different depths depending on the distance from the nipple as well as on the amount of subcutaneous fat. In the region of the areola the vessels form a periareolar arterial and venous plexus in intimate contact with the skin and gland proper. *b*₁, on the outer aspect of the breast, is at a deeper level than *b*, on the inner aspect, because of the presence of more adipose tissue on the external side.

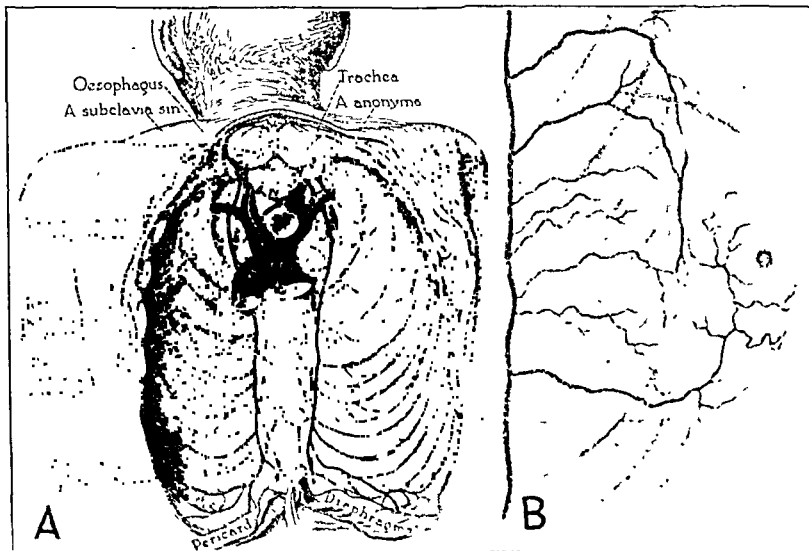


Fig. 5.—*A*, origin of internal mammary artery. The subclavian arteries, from which the internal mammary arteries originate, are shown on the inner aspect of the thoracic wall. Points at which the main perforating arteries pass through the intercostal spaces are indicated by arrows. (From Anson, B. J.; Wright, R. R., and Wolfer, J. A.: *Blood Supply of the Mammary Gland, Surg., Gynec. & Obst.* 69:468, 1939.) *B*, the injected internal mammary artery, showing the treelike ramification, consisting of five to seven branches having their origin in the deeper segment of the artery. These branches anastomose in an arch-shaped manner; most of them are subdivided along the mammary gland, sending ramifications to the thoracic lateral artery (Gitis and Livshits¹¹).

The degree of participation of these different sources in the vascularization of the gland, skin and nipple varies. It is important therefore, to consider the basic type and the variations for each source.

Vascularization takes place through at least two, and often three, main sources. The most frequent combinations are: (1) the internal mammary artery and the thoracic lateral artery (50 per cent); (2) the internal mammary artery and the intercostal arteries (30 per cent); (3) the internal mammary artery, the thoracic lateral artery and the intercostal arteries (aorta) (18 per cent).

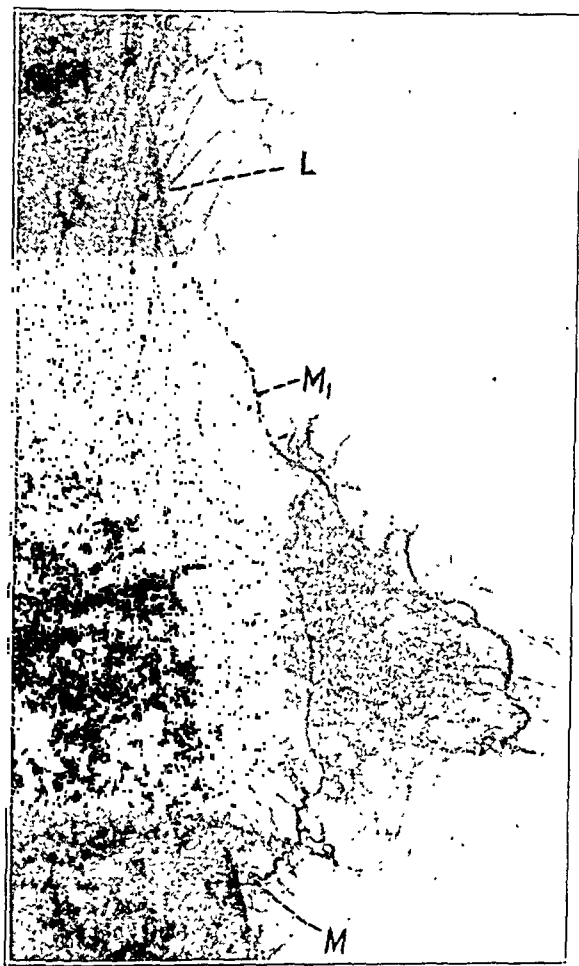


Fig. 6.—The spreading type of internal mammary artery, consisting of a few ramifications perforating mainly the second and, less frequently, the third intercostal space. The large perforating branch in the upper segment, after a short horizontal course, bends toward the nipple. *L*, thoracic lateral artery; *M*₁, main branch, internal mammary artery; *M*, posterior branch, internal mammary artery.

Combination of the thoracic lateral and the intercostal arteries, without the internal mammary artery, has not been encountered (table 1).

I. THE INTERNAL MAMMARY ARTERY (FIG. 5A)

The internal mammary artery has its origin in the subclavian artery in the neck and descends into the thorax behind the clavicle and the costal cartilages to the sixth intercostal space, where it is divided into its terminal ramifications.

Two types of branches are to be considered: namely, the anterior perforating and the posterior (with respect to the gland).

A. The Anterior Perforating Branches (figs. 5 B and 6).—The internal mammary artery sends perforating branches, usually six to eight, through the first to the fourth intercostal spaces—most frequently through the second, rarely through the first and fourth. From these perforating branches are derived the intercostal ramifications which run along the edges of the ribs, supplying the skin and muscles; the perforating branches become the main arteries of the gland.

The location of the main perforating branches is of definite practical import. When their origin is in the upper thoracic segment, the branches turn caudally toward the nipple after a short horizontal course. When their origin is deeper, the main artery branches out in a treelike manner (fig. 5 B).

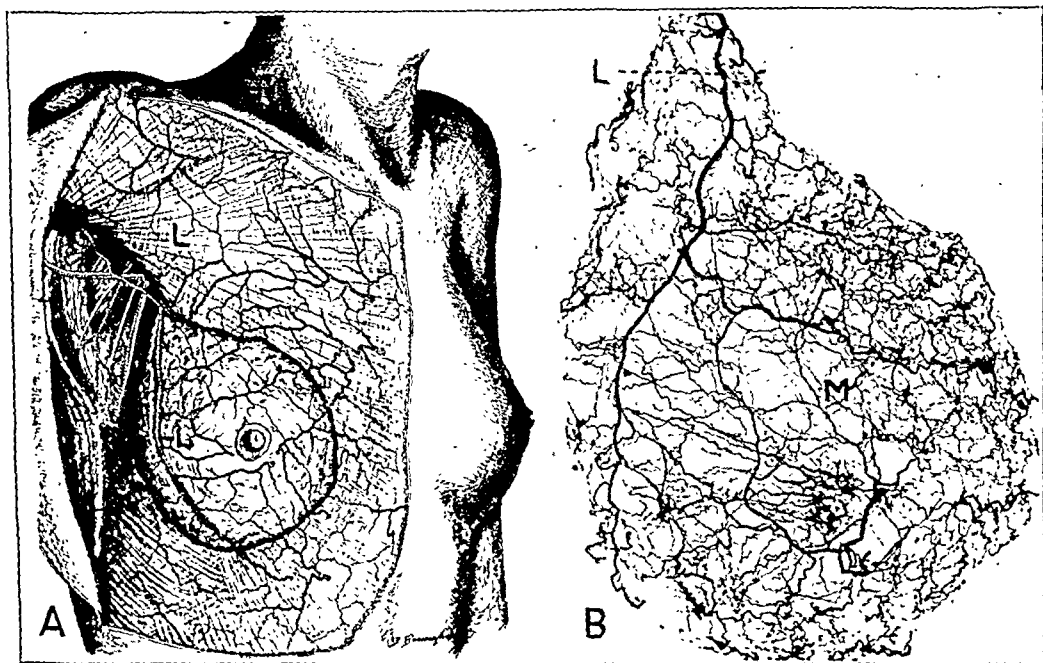


Fig. 7.—*A*, thoracic lateral artery and its topography (Salmon⁹). It originates from the external mammary artery and rarely from the axillary artery. Two main branches follow the external aspect of the gland. Note the numerous anastomoses above and below the nipple with the branches of the internal mammary artery. Its extraglandular topography, anterior to the neurovascular pedicle of the musculature, is shown. *L*, thoracic lateral artery. *B*, this figure represents the injected right breast of a young woman of 22, deprived of cutaneous covering and adipose tissue (Salmon⁹). The thoracic lateral artery (*L*) here is unusually well developed and by itself supplies more than half of the gland. The main perforating branch of the internal mammary artery (*M*) is small, only slightly larger than the other branches of the artery. Resection of the external half of the breast in this case would in all likelihood sufficiently disturb the blood supply of the nipple to bring about necrosis.

Two main types of variations are observed in the internal mammary artery. In the first, a few ramifications, perforating mainly the second and less frequently the third and fifth intercostal spaces, constitute the "spreading" type (fig. 6). Here the large perforating branch in the upper segment, after a short horizontal course, bends downward toward the nipple. From the angulation anastomotic branches are directed toward the external mammary artery. The main branch, at various distances from the nipple, sends out ramifications surrounding the

areola in the upper lateral and lower medial quadrants, forming an anastomotic ring. The second type is characterized by five to seven perforating branches, having their origin in the deeper segment of the artery. These branches form arch-shaped anastomoses. Most of the branches are subdivided along the mammary gland, sending numerous ramifications toward the thoracic lateral artery (fig. 5 *B*). A third intermediate type is sometimes observed in which types 1 and 2 are present.

B. The Posterior Perforating Branches (fig. 8).—The posterior aspect of the breast is approached by two or three arterial ramifications, mostly along the inner half of the gland. These branches are often wrongly considered as being derived from the aorta: anatomic studies consisting of careful roentgenographic examination of the injected vessels and dissection reveal that they arise from the internal mammary artery. Their disposition in the retromammary space and their origin are important in the evaluation of the posterior approach to the gland.



Fig. 8.—Same preparation as in figure 7 *A*, showing posterior aspect of breast. Note that the main retromammary arteries originate from the internal mammary artery. These arteries are long and penetrate the gland by short ramifications. This disposition permits easy retraction of the vessels in this area. *M*, internal mammary artery; *L*, thoracic lateral artery; *I*, intercostal artery (aorta); *IM*, inner intercostal artery (internal mammary artery).

One of these branches passes through the fourth intercostal space and the other through the fifth. They reach the posterior surface of the gland in the following way: The upper branch perforates the breast from behind forward and reaches the anterior aspect, where it anastomoses with the branches of the thoracic lateral artery. The inferior branch is long and sends short ramifications into the gland; it is easily retracted during exposure of the gland's posterior aspect.

II. THE THORACIC LATERAL ARTERY

Descriptions of this vessel vary greatly. The resultant incorrect deductions are responsible for some of the surgical procedures which deprive the gland of its essential blood supply¹⁴ (fig. 2).

14. Biesenberger, H.: Eine neue Methode der Mammaplastik, *Zentralbl. f. Chir.* 57:2971, 1930.

As a rule the size of the thoracic lateral artery is dependent on the development of the internal mammary artery (fig. 7 B). Although the majority of authors agree in principle as to the important role of the latter in vascularization of the breast, similar agreement does not seem to prevail with regard to the thoracic lateral artery. Rouvière, one of the outstanding anatomists of the present day, pointed out that the extensive development of the mammary lymphatics and the close parallelism in the development of the lymphatic, venous and arterial systems indicate that the thoracic lateral artery participates abundantly in the vascularization of the central parts of the gland. This contradicts the views of Manchot and his followers, who maintained that the thoracic lateral artery scarcely participates in the blood supply of the gland and does not provide branches for the nipple. Undoubtedly more reliance can be placed on the findings of later

TABLE 1.—*Distribution of the Main Arteries of the Breast**

Main Arteries	Origin	Main Types of Ramifications	Extent of Participation	Region Supplied	Depth	Periareolar Circulation
Internal mammary artery (figs. 5B, 6 and 8)	Subclavian artery	(1) 5 to 8 perforating branches; (2) one main branch through 2d or 3d intercostal space	Largest in size and length; constant participation	Main blood supply of gland in majority of cases	0.5 to 1 cm. subcutaneously depending on amount of fat present	Predominant in vascularization of areola and nipple in majority of cases
Thoracic lateral artery (fig. 7)	External mammary artery; rarely originates directly from the axillary artery	Two parallel branches on lateral aspect of breast	Second in size, varied, depending on development of internal mammary artery; in 13 per cent of cases predominant in vascularization of gland and nipple	External half of breast; maintains balance with internal mammary artery	1 to 2.5 cm. depending on amount of fat on external aspect	In 13 per cent of cases constitutes main supply to areola and nipple
Intercostal arteries (figs. 4 and 8)	The inner group originates from the internal mammary artery, the outer group from the aorta	The inner group has 2 to 3 ramifications to the posterior aspect of the gland; the outer group is less important	Anastomotic plexus in lower quadrants mostly on account of inner intercostal arteries; a main perforating branch directly into the nipple is often present	Lower quadrants; sometimes areola and nipple through a direct perforating branch	Retromammary space	Mainly through a direct perforating branch

* These data are based on dissection and study of roentgenograms of injected vessels in 104 female breasts.

investigators, like Rouvière, who could visualize the fine branches of the anastomotic plexuses of the gland and nipple by roentgenographic studies.

Marcus¹³ revealed that the thoracic lateral artery participates in vascularization of the nipple in 55 per cent of cases and of the gland in 68 per cent (table 1).

Gitis and Livshits¹¹ found constant participation of the thoracic lateral artery in the vascularization of the skin, gland and nipple. They stated that the size of the artery varies and is frequently dependent on the development of the internal mammary artery.

The thoracic lateral artery, also called the principal external artery, takes its origin from the external mammary artery, a branch of the axillary. It rarely is derived from the axillary artery (fig. 7 A).

In its extraglandular course the thoracic lateral artery is situated anterior to the perforating branch of the third intercostal nerve and the neuromuscular pedicle. When it arises from the external mammary artery, as occurs most frequently, it rapidly abandons the posterior aspect of the pectoral muscle.

Its caliber varies from 1 to 2 mm., according to the size of the gland. It is directed obliquely downward, inward and forward from the axilla, first toward the axillary prolongation of the gland and then following its anterior aspect, often in contact with the gland near the external border and terminating at the lower level of the gland in its final branches. This area is rich in subcutaneous fat and is abundantly vascularized.

The common type shows two branches which run parallel to the lateral aspect of the gland. One branch is always more developed than the other. The medial branch is deflected toward the medial side near the nipple to form an anastomosis with branches of the internal mammary artery. The lateral branch turns medially below the nipple, and usually sends branches into the nipple directly or through anastomosis with other arteries (fig. 7A).

Terminal branches consist of two or three ramifications which often penetrate into the gland and pass under the nipple for anastomosis with the intercostal arteries.

III. INTERCOSTAL ARTERIES

There is a lack of agreement as to the origin of the intercostal arteries which supply the breast. Salmon⁹ considers the inner intercostal arteries, which penetrate the fourth and fifth intercostal spaces, as posterior branches of the internal mammary artery (fig. 8). Only the external intercostal arteries originate in the aorta and their glandular ramifications are not very numerous, varying in size and direction. They are located on the pectoral aponeurosis at the external aspect of the gland and form an anastomotic plexus in the lower quadrant with the ramifications of the internal mammary artery on the inside and of the thoracic lateral artery on the outside. From this plexus derive branches going toward the areola and nipple. As a rule, however, external intercostal arteries do not participate to a great extent in the blood supply of the gland and nipple, unlike the inner intercostal arteries, deriving from the internal mammary artery. To the latter group also belongs an intercostal perforating branch, not always present, which penetrates through the entire depth of the gland, enters the nipple directly and fans out around the areola (fig. 4). The intercostal arteries do not interfere with the easy separation of the gland from the retromammary space, as they usually run along the pectoral fascia and show short terminal branches.

RELATIONSHIP OF THE MAIN SOURCES OF BLOOD SUPPLY TO THE AREOLA AND NIPPLE

The central portion of the breast is particularly liable to necrosis in certain surgical procedures. It is therefore important to consider the topography of the vascular ramifications in this area (fig. 10).

The branches of the three main sources of blood supply, in approaching the gland, form two anastomotic plexuses, one superficial and the other in the depths of the gland. From these two plexuses ramifications extend toward the surface and the base of the nipple and the areola. There are many variations in these periareolar anastomoses, and certain basic types and abnormalities can be discerned. Their comprehension is essential to safe surgical intervention in this region.

I. CIRCULAR PERIAREOLAR PLEXUS (FIG. 10A)

In this group the ramifications form a nearly complete ring around the nipple. The width of the ring varies between 2 and 5 cm.; it is formed by ramifications of the internal mammary artery in the inner upper angle, the thoracic

lateral artery at the outer upper angle and the intercostal arteries below. The branches of the internal mammary artery, which predominate, are divided at different distances from the nipple into two ramifications which encircle it, together with branches from the other sources. From this vascular ring fine arterioles reach the base of the nipple and the areola. This type of vascularization assures the maximum blood supply and can be considered the safest from the viewpoint of possible necrosis. It was found in 70 to 74 per cent of the breasts examined (table 2). Resection of the external half of the breast will not compromise the vitality of the nipple in the presence of circular periareolar vascularization. This is particularly true in cases in which the thoracic lateral artery participates but slightly in the formation of the plexus.

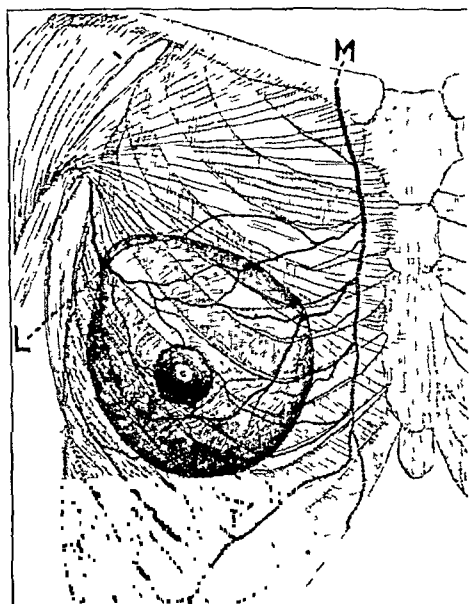


Fig. 9.—Diagram of the main vascular pedicles of the breast illustrating the present concept of its blood supply. Note the numerous anastomotic branches between the two main vessels and the periareolar plexus. The deeply located parts of the arteries are represented in dotted lines. *M*, internal mammary artery; *L*, thoracic lateral artery; *I*, intercostal arteries.

TABLE 2.—Varieties in Periareolar Vascularization

Type	Origin	Ramifications	Relationship to Surgery	Frequency
1. Circular plexus (fig. 10A)	Usually the two main sources with predominance of the internal mammary artery	Assure maximum blood supply to nipple by extensive circular anastomosis	Safest	70 to 74 per cent of cases
2. Loop plexus (fig. 10B)	Thoracic lateral artery predominant; participates with other sources of blood supply to formation of a loop	Derive mostly from the thoracic lateral artery	Extensive lateral resection of the gland may deprive the nipple of adequate circulation and result in necrosis	20 per cent of cases
3. Radial plexus (fig. 10C)	Lack of anastomosis between two main sources; thoracic lateral artery and internal mammary artery	Characterized by absence of anastomotic branches between the main sources of blood supply	Deep periareolar incision will result in necrosis of corresponding part	6 per cent of cases

II. LOOP TYPE PLEXUS (FIG. 10B)

This is observed when the thoracic lateral artery is the most developed. Its branches turn medially above and under the nipple, anastomosing with the ramifications of the lesser sources of blood supply. The periareolar plexus originates from this loop.

This type has been observed in about 20 per cent of the breasts examined. Extensive resection of glandular tissue vascularized by the thoracic lateral artery may result in necrosis of the central parts of the gland (table 2).

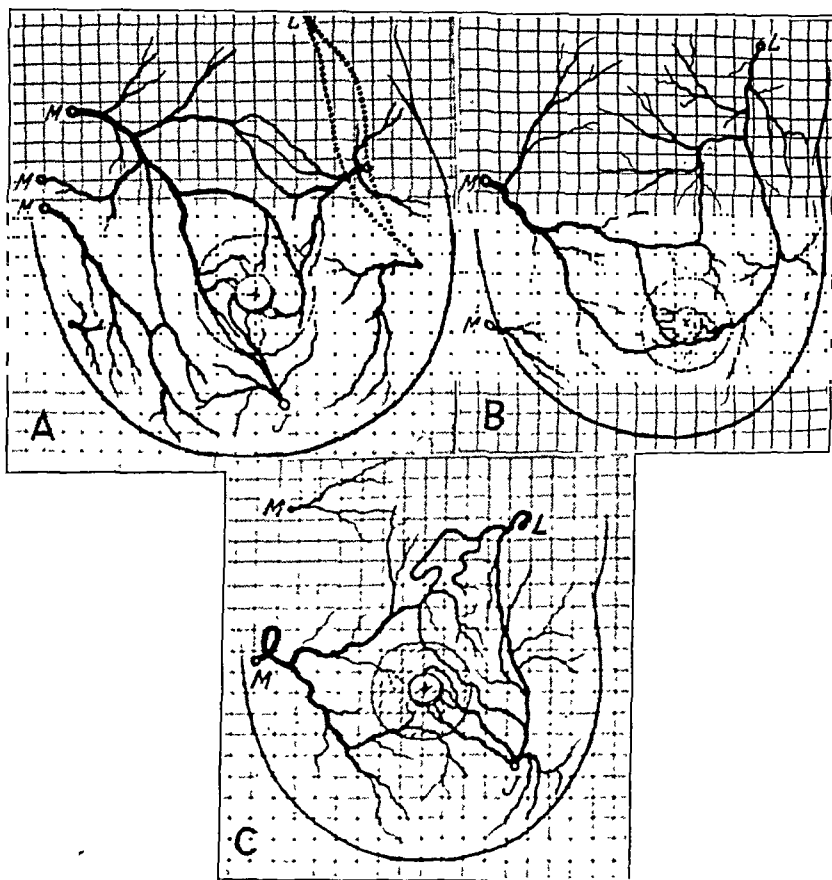


Fig. 10—*A*, circular periareolar plexus (Marcus¹³). The ramifications of the main arteries form a complete ring around the nipple. This type of vascularization assures maximum blood supply and is the safest from the viewpoint of possible necrosis. It is found in about 70 to 74 per cent of cases. The internal mammary artery is well developed. Resection of the external half of the breast, sacrificing the thoracic lateral artery, will not compromise here the vitality of the central portion of the gland. *M*, internal mammary artery; *L*, thoracic lateral artery; *J*, intercostal arteries. *B*, the loop type of periareolar plexus, observed when the thoracic lateral artery is predominant. The branches from both sources anastomose above and below the nipple, forming a loop. This type is found in about 20 per cent of cases. Wide external resection of the gland is liable to disrupt the blood supply of the central portion. *M*, internal mammary artery; *L*, thoracic lateral artery. *C*, radial type of periareolar plexus. This type is characterized by the lack of any ring or loop formation around the nipple. The ramifications of the main arteries are directed toward the nipple without anastomosis between them and their arterial pedicles. This type of plexus is found in 6 per cent of cases. Resection of any extensive amount of the lateral part of the breast will unavoidably be followed by necrosis of the nipple. *M*, internal mammary artery. *L*, thoracic lateral artery; *J*, intercostal artery.

III. RADIAL TYPE PLEXUS (FIG. 10C)

This is the least frequent type, observed in about 6 per cent of the total number of breasts. It is characterized by lack of any ring or loop formation around the nipple. The ramifications from the two main sources are directed toward the nipple at a distance from each other without anastomosis between them and their main arterial pedicles. With this type of plexus a deep circular incision in the areolar zone will necessarily sever the main sources of blood supply to the corresponding parts of the breast. An exception might occur if the perforating intercostal artery (branch of the internal mammary artery) reached the nipple directly from the posterior aspect of the gland (fig. 4). This branch, however, is not always present, and in fact was usually observed to be missing in the radial type of ramification.

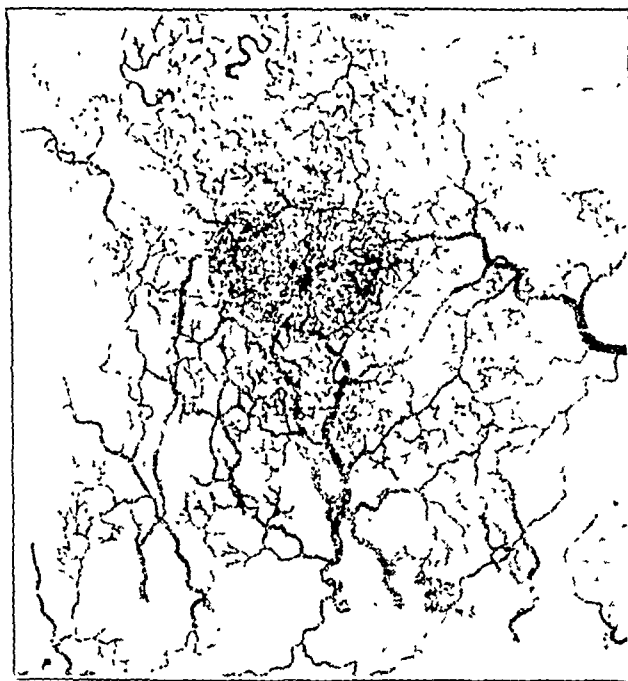


Fig. 11.—Disposition of the venous and arterial plexus around the areola. This plexus is highly developed and superficially located between the skin and gland proper without presence of fat. The preservation of these two plexuses is essential for avoidance of necrosis and requires superficial dissection of skin when transposition of the nipple is done.

As it is impossible to foresee which type of vascularization will be encountered, all types must be kept in mind in evaluating any reconstructive procedure.

DEPTH OF THE VESSELS IN RELATIONSHIP TO THE CUTANEOUS COVERING AND THE GLAND PROPER

The mammary vessels, as derivatives of cutaneous arteries, are located in the subcutaneous layer. Their depth depends on the amount of fatty tissue present: in fatty hypertrophies they are found at a deeper level than in the atrophic types (fig. 4). As the mammary arteries are tortuous, they permeate the perimammary fat at various levels, and are accompanied in their trajectories by corresponding veins and lymphatics.

1. The origin of the main perforating branches of the internal mammary artery is found at a distance of 1 to 1.5 cm. from the border of the sternum. Anteriorly their ramifications are found at a depth of 0.5 to 1 cm., depending on the thickness of the fat layer. They are often visible under the skin.

2. The main branches of the thoracic lateral artery are usually located at a deeper level, from 1 to 2.5 cm., because of the greater amount of fat present on the external aspect of the breast.

3. In approaching the areolar region, the blood vessels become more superficial and lie closer to the gland. In their course, they send forth arterioles toward the gland and the skin, forming a deep and a superficial plexus. The position of these plexuses is determined by the relationship between the gland and the cutaneous skin covering (fig. 4). In a sagittal section of the normal breast, the cutaneous surface appears half round and the gland cone shaped. The apex of the cone joins the cutaneous surface at the level of the nipple. Thus a heavy fatty layer is present between the gland and the skin at the periphery, gradually thinning out toward the center and disappearing entirely at the level of the areola, where skin and gland are in intimate contact. Here the periareolar plexus is very superficial, being covered only by the fine areolar skin. The preservation of the arterial and venous plexuses is imperative for the prevention of necrosis in this area (fig. 11). Circular incisions made here should be intradermal and the dissection of the skin superficial.

SYMMETRY OF VASCULARIZATION

Most investigators agree that symmetric vascularization of both breasts is rare. This is evident from study of roentgenograms of pairs of breasts. It explains the occurrence of unilateral necrosis where identical surgical procedures are used on both sides (fig. 7 B).

SUMMARY AND CONCLUSIONS

Accurate knowledge of the vascularization of the breast is essential to the avoidance of necrosis in mammoplasty.

Most descriptions of the mammary blood supply by older anatomists were based solely on dissection and thus did not reveal the minute vascular ramifications observed by later investigators in roentgenographic studies of injected vessels. The data presented here are based on dissection and roentgenographic studies of injected vessels in 103 female breasts.

The blood supply of the breast is derived from at least two and often three of the following main sources: (a) the internal mammary artery, (b) the thoracic lateral artery and (c) the intercostal arteries (aorta). The most frequent combination is that of the internal mammary artery and the thoracic lateral artery (50 per cent).

A balance is usually maintained between the two main internal and external vascular pedicles. The internal mammary artery is always present. In approximately 55 per cent of the cases the thoracic lateral artery has an equal part with the internal mammary, and in 13 per cent a predominant part, in vascularization of the gland, areola and nipple.

The ramifications of the three main arteries of the breast participate in the formation of a superficial and a deep periareolar plexus, of which there are three basic types:

(a) The circular plexus (74 per cent) provides the safest vascularization for the nipple and areola.

(b) The loop type (20 per cent) occurs when the thoracic lateral artery is predominant.

(c) The radial type (6 per cent) has periareolar ramifications from the two main arteries, directed toward the nipple without anastomoses. Circular incision around the nipple in this type is likely to sever the blood supply and result in necrosis.

As it is impossible, prior to operation, to foresee the type of vascularization present in the living person, all surgical procedures based on wide resections of mammary structures with ligation of large vascular branches must be considered to involve the danger of necrosis.

The surgical procedure of choice must preserve the blood supply in all types of vascularization.

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ADVENTITIOUS BURSAS

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So-called adventitious bursas are encountered frequently, but a review of the literature indicates that they are poorly understood. Most authors disagree as to the pathogenesis and histologic appearance of such bursas.

In 1890 Schuchardt¹ stated that hygromas could develop anywhere in connective tissue independently of previously formed connective tissue spaces. He explained the formation of subcutaneous hygromas on the basis of inflammation, since he found fibrin in inflamed connective tissue. He thought that the fibrin



Fig. 1.—Adventitious bursa from the soft tissues over the medial aspect of the head of the first metatarsal bone. The cystic cavity in the center is apparent.

was a part of a liquefaction process that continued until the eventual formation of multilocular small sacs and the subsequent degeneration of the separating walls. He said that the peculiar fibrinous inflammatory process could be recognized in old hygromas only in the wall of the sac and could be followed for a considerable depth. In these regions he found that the nuclei were divided and the cells swollen as they are in coagulation necrosis.

Hammar² in 1894 expressed the opinion that the lining of the subcutaneous bursa was connective tissue and not endothelium.

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Abridgment of a thesis submitted by Dr. Buck to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Orthopedic Surgery.

1. Schuchardt, K.: Ueber die Entstehung der subcutanen Hygrome, *Arch. f. klin. Chir.* 40:606-609, 1890.

2. Hammar, J. A.: Ueber den feineren Bau der Gelenke, *Arch. f. mikr. Anat* 43:266, 1894; cited by Jones.¹⁰

Dömény³ in 1897 said that superficial bursas developed in a deep loose stratum of subcutaneous tissue and that the connective tissue in the region of embryonic bursas had a peculiar swollen appearance like gelatin. He noted that the olecranon bursa of a baby aged 2 months had two connective tissue spaces under the layer

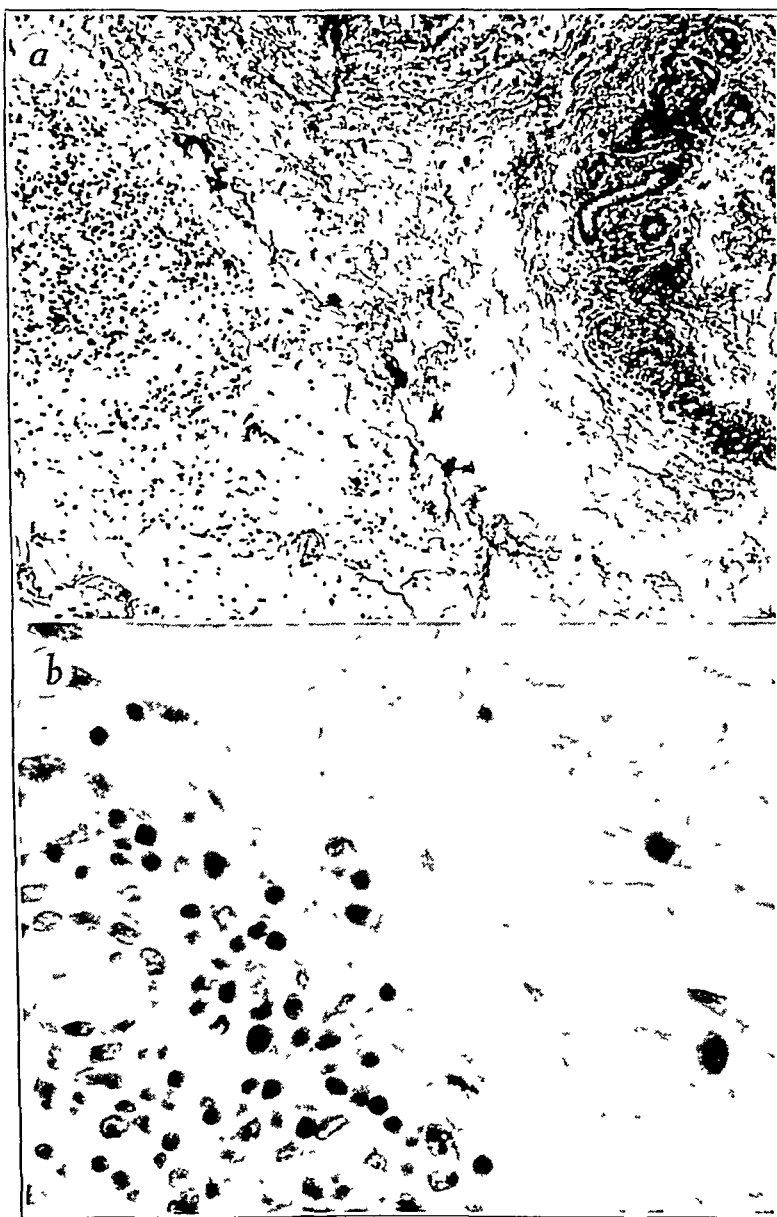


Fig. 2.—Sections of connective tissue in the medial aspect of the first metatarsal bone showing numerous small capillaries and an inflammatory reaction consisting mostly of lymphocytes but situated for the most part in a perivascular arrangement: (a) stained with hematoxylin and eosin ($\times 75$), (b) stained with hematoxylin and eosin ($\times 500$)

of fat and that the bursa did not become distinct until the fat about the elbow disappeared

³ Domény, P. . *Entwicklung und Bau der Bursae mucosae*, Arch f Anat u Entwicklungs-gesch., 1897, pp. 295-306

In 1903 Langemak⁴ reviewed the existing literature on bursas and disagreed with Schuchardt. He expressed the opinion that the gelatinous material in bursas was purely degenerative instead of a fibrinous exudate. He said that this degenerative material was "fibrinoid" and that the distinguishing feature was that it stained yellow with Van Gieson's stain instead of pink, as connective tissue usually does.

Virchow,⁵ as quoted by Churchman,⁶ said: "The bursae are in no sense true serous sacs, . . . but are rather places where the connective tissue, originally present in continuo, forms spaces by a process of atrophy and where these spaces come, in time, to be independent cavities."

Clark⁷ in 1908 described an adventitious bursa that had been removed from the surface of an amputated hammer toe. He said that a small amount of glairy

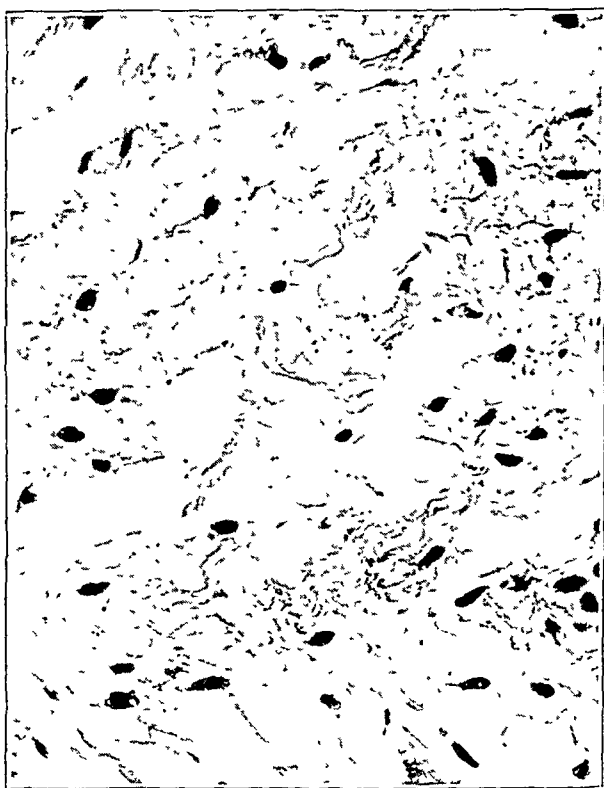


Fig. 3.—Connective tissue from the medial aspect of the first metatarsal bone showing separation of the collagen fibrils, swelling caused by a mucus-like material and also by fibroblasts. (Stained with hematoxylin and eosin [$\times 365$].)

fluid escaped when the bursa was sectioned. The microscopic picture was that of a finely fibrillated tissue supported by a poorly stained framework of connective tissue. He found no nuclei or distinct cell bodies in the lining itself, and the tissue in the lining was similar to tissue frequently seen adjoining regions of cystic degeneration in fibromas.

4. Langemak, O.: Die Entstehung der Hygrome, *Arch. f. klin. Chir.* **70**:946-972, 1903.

5. Virchow, cited by Churchman.⁶

6. Churchman, J. W.: Luetic Bursopathy of Verneuil, *Am. J. M. Sc.* **138**:371-396 (Sept.) 1909.

7. Clark, W. C.: The Pathogenesis of Ganglia, with a Description of the Structure and Development of Synovial Membrane, *Surg., Gynec. & Obst.* **7**:56-78 (July) 1908.

Sutton⁸ in 1922 explained the formation of bursas as a rupture of the intermediate connective tissue over a bony prominence. He said that the connective tissue became filled with fluid and the wall was formed by the thickened connective tissue. Hertzler⁹ in 1923 discussed the inflammation of deep calcaneal bursas and voiced the opinion that pressure caused the formation of subcutaneous or any other type of bursas.

In 1930 Jones¹⁰ made an extensive study of cystic bursal hygromas and found that the walls of prepatellar bursas consisted of two main layers, an external and an internal. He said that the external layer was composed principally of moderately loose, white fibrous connective tissue including vascular fat lobules. Some

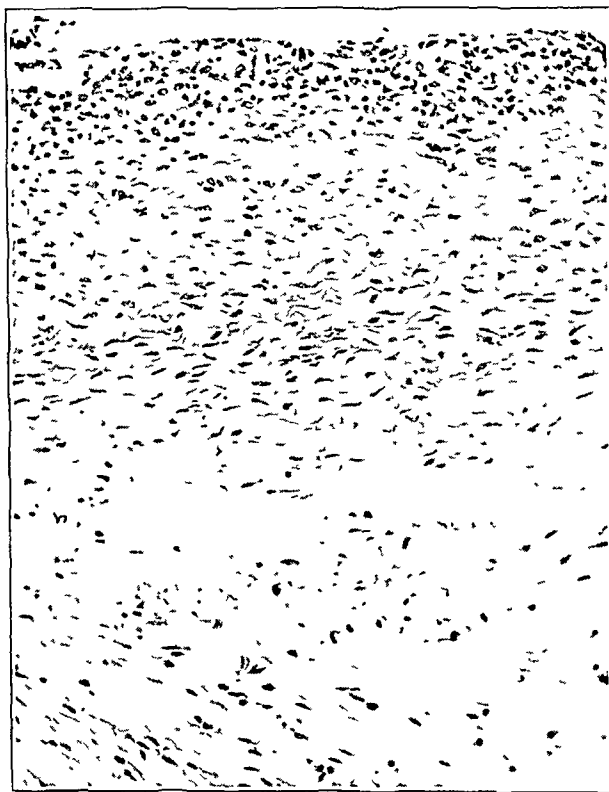


Fig. 4—The wall of an adventitious bursa from the medial aspect of the first metatarsal bone; the fibroblasts are flattened and there is a concentric arrangement around the bursal cavity (Stained with hematoxylin and eosin [$\times 130$])

of the fat lobules showed signs of atrophy with proliferation of young connective tissue. The internal layer was composed of connective tissue, which evidently was proliferating and rich in capillaries. Toward the center of the cavity there were connective tissue cells with a great quantity of collagen fibers between the cells. The nuclei were observed to be necrotic, and degeneration was noted in other regions.

8 Bland-Sutton, J Tumours, Innocent and Malignant Their Clinical Characters and Appropriate Treatment, London, Cassell & Co, Ltd, 1922

9 Hertzler, A. E Inflammation of the Deep Calcaneal Bursa, J A M. A. **81**:8-9 (July 7) 1923

10 Jones, H T Cystic Bursal Hygromas, J Bone & Joint Surg **12**:45-89 (Jan) 1930

Roberts¹¹ in 1929 studied the pads of fat over calcaneal spurs and observed that the masses of fat were surrounded by delicate stromas of connective tissue which were grouped together by membranous partitions, so that a loosely connected layer was formed in which the spaces seemed to be filled with lymph. He accepted the theory that bursas are enormously distended lymph spaces.

EMBRYOLOGIC ASPECTS

Material.—The material for this study was secured from specimens removed at the time of plastic repair of the head of the first metatarsal bone for hallux valgus deformity and bunions. Approximately 270 specimens were examined, and

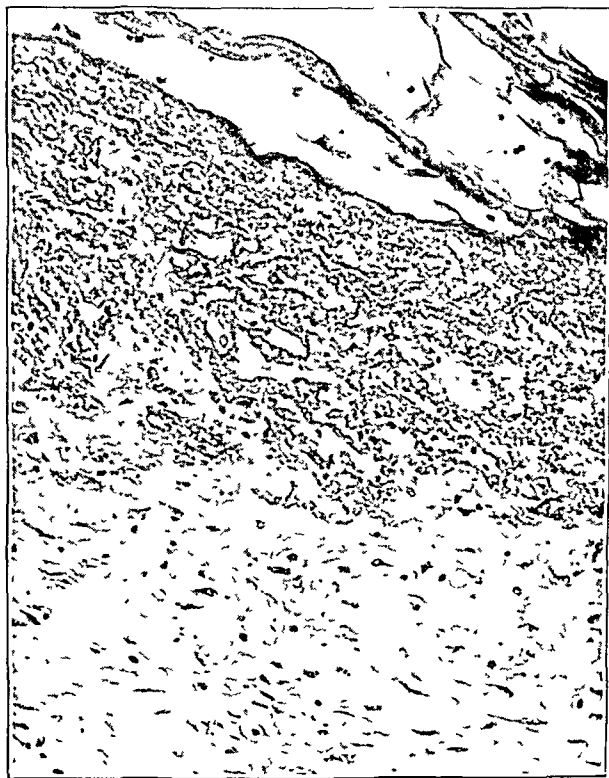


Fig. 5.—Adventitious bursa from the medial aspect of the first metatarsal bone. The wall of the cavity contains swollen fibroblasts with mucoid or myxomatous degeneration; the central portion is practically acellular and is made up of a homogeneous staining mucoid material (Stained with hematoxylin and eosin [$\times 50$].)

sections of bursas were taken when they were present. Bursas were found in all stages of development; some contained large cystic cavities (fig. 1); others contained small cavities, and still others contained none at all. Included in this series was one bursa of the external malleolus and one removed from the foot. For comparison, several prepatellar bursas were examined. One specimen of a true bursa removed from the popliteal space was studied.

On all tissue studied, the following stains were used: hematoxylin and eosin, mucicarmine, the Mallory-Heidenhain aniline blue stain, Van Gieson's stain and elastin H.

11. Roberts, P. W. Bursitis of the Foot—A Neglected Cause of Disability. *Am J Surg* 6:313-317 (March) 1929

Results.—The histologic changes which were found in these adventitious bursas of the feet may be classified as early and late. Early changes can arbitrarily be taken as those which are apparent in the connective tissue of the affected region but which have not resulted in the formation of actual liquid mucoid material. Late changes are those which have resulted in the formation of an actual cavity which contains the mucoid material typical of bursas.

In the region surrounding beginning or early bursal formation, an increased number of blood vessels constantly was present in the connective tissue. These vessels consisted of small capillaries. In and around these newly formed blood vessels were usually to be found numerous lymphocytes and occasionally a polymorphonuclear leukocyte (fig. 2).

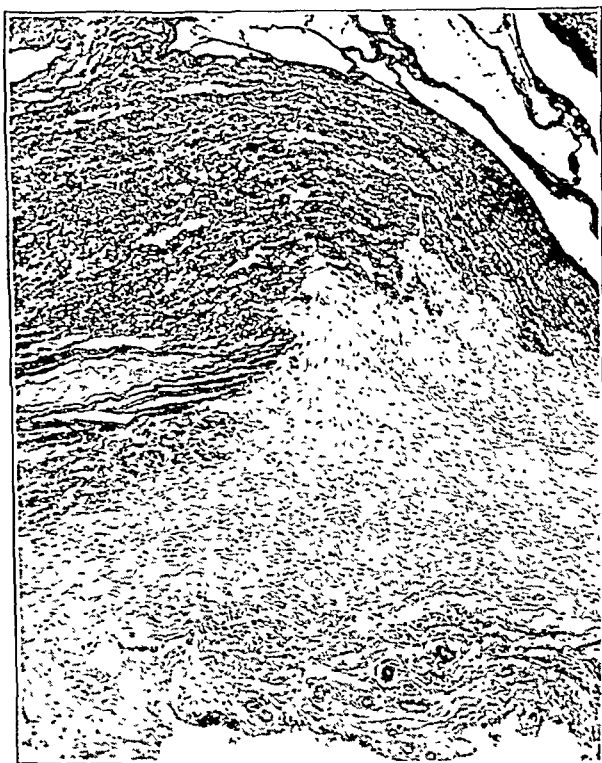


Fig. 6.—Adventitious bursa from the medial aspect of the first metatarsal bone stained with mucicarmine stain, showing affinity of the mucoid material in the cavity for carmine ($\times 45$).

The fibroblasts and collagen fibrils in the vicinity where the bursal cavity was about to form became swollen and separated by a mucus-like material which stained not at all or, at the most, faintly bluish with hematoxylin and eosin and contained no cells (fig. 3). The collagen in this region did not stain as strongly reddish with Van Gieson's stain as did the collagen fibrils peripheral to this region. The results of staining with mucicarmine were negative at this stage.

In sections of well formed adventitious bursas, that is, those in which there was an actual cavity filled with mucoid material, the new blood vessels and the inflammatory cells were evident in the connective tissue of the wall of the cyst. Toward the cavity, the myxomatous or mucoid degeneration became more marked. The fibroblasts and collagen fibrils became more swollen and finally disappeared. The fibroblasts and collagen fibrils which remained around the cavity assumed

a flattened appearance and were arranged concentrically (fig. 4). The central mucoid material in the cyst contained no collagen fibrils and no cells (fig. 5). In the vicinity of the cystic cavity the collagen fibrils eventually lost their affinity for the fuchsin in the Van Gieson stain. As more mucoid material formed between

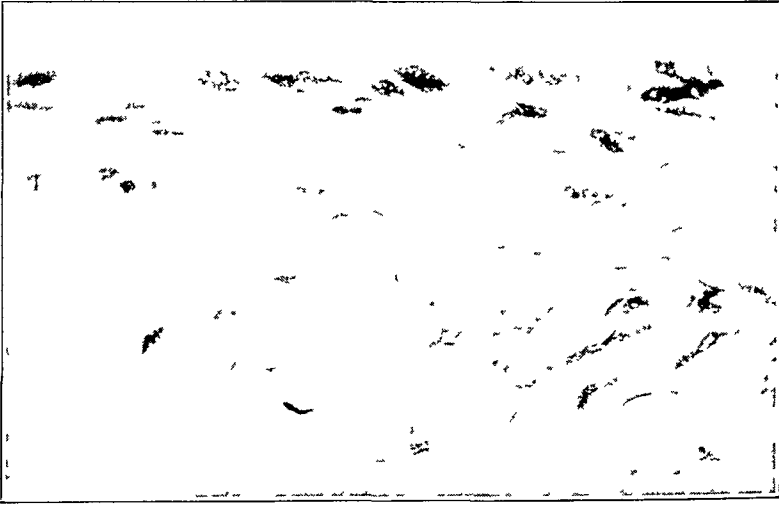


Fig 7—Wall of an adventitious bursa from the medial aspect of the first metatarsal bone. The flattened fibroblastic cells simulate endothelial cells. (Stained with hematoxylin and eosin [$\times 300$])

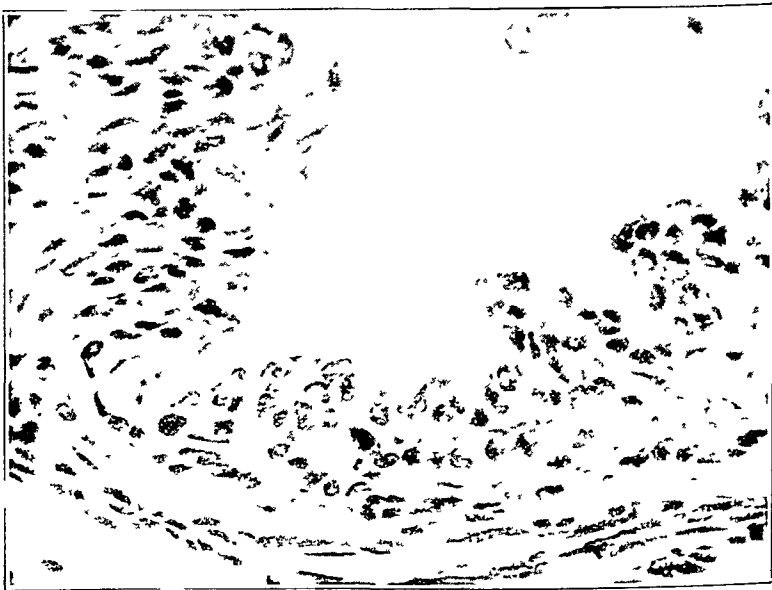


Fig 8—True bursa from the popliteal space. The lining endothelial cells are thrown in folds; there is no mucoid or myxomatous degeneration of the connective tissue in the wall of the cavity. (Stained with hematoxylin and eosin [$\times 420$])

the connective tissue fibrils, the mucicarmune stain became slightly positive, until in the central cystic region it was very strongly positive (fig. 6). In no specimen of these adventitious bursas could lining cells be found which could be interpreted

as endothelial cells. In certain specimens where well formed cysts were apparent, flattened cells lined the cavity. It would appear to be more logical to consider these as flattened fibroblastic cells than as endothelial cells (fig. 7).

The histologic study of the prepatellar bursas revealed throughout exactly the same changes observed in the adventitious bursas obtained from bunions. Evidently they also are adventitious, not true bursas. In contrast, a bursal cavity removed from the popliteal space was lined with endothelial cells which were very distinct and arranged in a villous formation suggestive of synovial lining (fig. 8). There was no evidence of myxomatous or mucoid change in the connective tissue surrounding the endothelium. Van Gieson's stain revealed that the collagen fibrils were plentiful surrounding bursas. The mucicarmine stain revealed small amounts of mucus-like material in the lining cells. The probabilities are that the bursal cavity was directly connected with the knee joint. The connection is suggested by the similarity between the lining endothelium of this bursa and the synovium of the joint.

COMMENT

This study was undertaken in order that the development and pathogenesis of adventitious bursas might be better understood. As found in most of the textbooks, the definition of a bursa is inconstant and the meaning and description not clear.

In the development of adventitious bursas, it would appear that the first finding in the region where a bursa is about to develop is a myxomatous change of the connective tissue. Adventitious bursas are not present at birth. Trauma undoubtedly plays a major role in their formation. Unlike earlier writers, we do not believe that bacterial inflammation is the primary cause for the development of the adventitious bursas, in spite of the fact that collections of lymphocytes and polymorphonuclear leukocytes are found around the affected region. Degeneration is probably the factor which brings out these so-called inflammatory cells. What frequently is described by the surgeon as a bursa is myxomatous mucoid degeneration and cystic formation in connective tissue. Frequently there is more than one focus of myxomatous degeneration. These foci progressively grow larger and eventually coalesce.

The material present in the cavity of an adventitious bursa is of an indeterminate mucoid nature. It is the same material which was referred to by Langemak as fibrinoid. In its staining qualities and character it differs from mucus formed by epithelium. Its formation is a degenerative rather than a secretory process occurring in benign or malignant mesodermal tissues. Exactly what it represents is an enigma. In contrast to an adventitious bursa, a real bursa has an endothelial lining and does not exhibit any myxomatous change. Probably most of the true bursas are connected with joint cavities.

SUMMARY AND CONCLUSIONS

Adventitious bursas develop in fibrous connective tissue. They are not present at birth but are acquired. The process is one of mucoid or myxomatous degeneration of connective tissue. It appears to be degenerative rather than secretory. Repeated trauma to soft tissue over a bony prominence seems to be the causative factor. Adventitious bursas have no true lining, while true bursas have an endothelial lining.

EFFECT OF SULFATHIAZOLE ADMINISTERED ORALLY AND SULFANILAMIDE IMPLANTED LOCALLY ON CONTAMINATED WOUNDS

EXPERIMENTAL STUDY

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AND

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During a study¹ of the nonsuture method of bridging a gap in the severed femoral artery of the dog, data were accumulated concerning the value of sulfanilamide implanted locally into the wound and also concerning the usefulness of sulfathiazole administered orally. Although the number of the experiments in which analysis of the data has been made is not large, the extensive nature of the experimental procedure plus the controlled condition of the operations make it worth while to report the results.

METHOD

After some 80 preliminary operations an exact technic was adopted, and with the time relations standardized a series of 30 carefully controlled operations were performed. In 20 animals the following procedure was followed: The right femoral artery was exposed under unsterile conditions, the incision being exactly 10 cm. in length. The artery was isolated for 2 cm. and divided between transfixion ligatures. All bleeders were clamped and tied with fine silk ties. Twenty-four hours later the animal was again anesthetized, intravenously administered pentobarbital sodium being the anesthetic agent, and after preliminary irrigation of the femoral wound on the right side with saline solution a 10 to 12 cm. segment of the left femoral vein was removed under aseptic conditions. The vein was set aside, care being taken to keep it sterile, and the femoral wound on the right side was excised completely, the operation including débridement of the ends of the artery. All bleeders were tied with arterial (B-1 Deknatel) silk. The wound was then irrigated with 250 cc. of saline solution and redraped. The two tube nonsuture technic was then carried out, vitallium tubes 3 mm. in outside diameter being inserted into the segment of the left femoral vein (fig. 1). The wound was closed carefully with interrupted sutures of arterial silk to the deep fascia and muscle and to the superficial fascia. The skin was not sutured, but the cut edges usually fell together as a result of the careful approximation of the superficial fascia. A collodion gauze dressing was applied. Postoperatively the wound was examined daily and the nature of the healing observed, as well as the pulsation of the venous segment and the distal artery. At the end of seven days all of the wounds were opened and the anastomoses examined to determine blood flow. The condition of the wound was carefully noted and the anastomosis resected and examined grossly for thrombosis.

With 10 animals exactly the same procedure was carried out as with the aforementioned group except for the substitution of the Carrel suture technic for the anastomosis of the

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The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Cornell University Medical College.

1. Blakemore, A. H.; Lord, J. W., Jr., and Stefkó, P. L.: The Severed Primary Artery in the War Wounded, *Surgery* **12**:488-508 (Sept.) 1942; Restoration of Blood Flow in Damaged Arteries: Further Studies on a Nonsuture Method of Blood Vessel Anastomosis, *Ann. Surg.* **117**:481-497 (April) 1943.

segment of vein to the cut ends of the right femoral artery. A second variation was that the wounds were studied for fourteen days instead of seven, because it had been observed in earlier series that with the Carrel method secondary hemorrhage or thrombosis might occur during the second week. With the nonsuture method failure, if it is going to occur, does so during the first seven days.

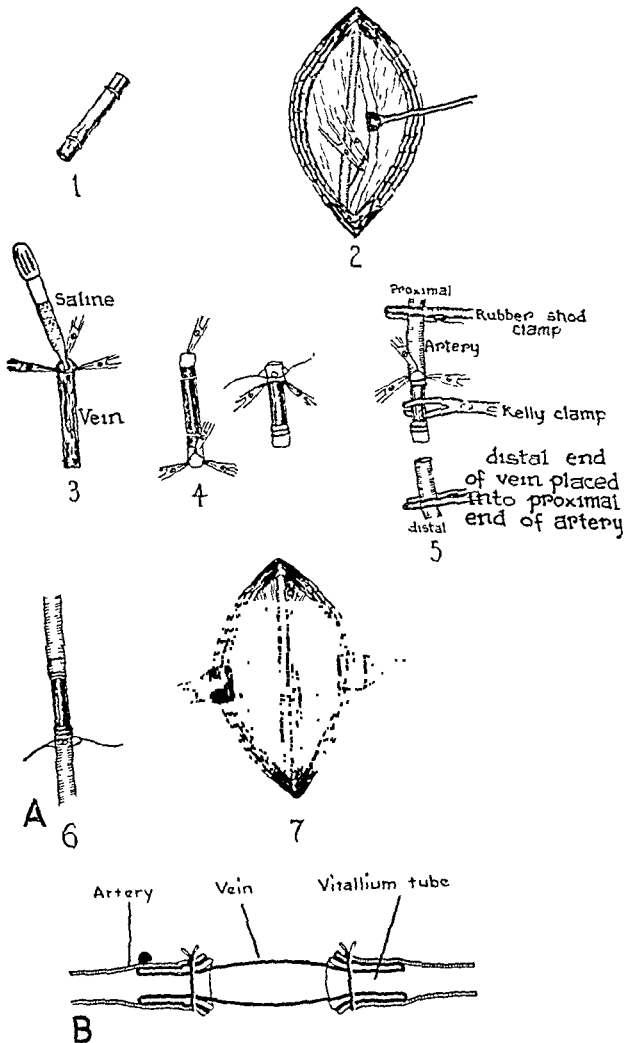


Fig. 1.—4, the various steps in the operation as carried out in the femoral artery: 1 shows the vitallium tube with its two ridges (sometimes grooves). 2 shows the artery and vein exposed. The vein is retracted and clamps have been placed upon a branch. We now think it is perhaps better technic to ligate the branch first, clamp distally and cut between. In 3, the segment of vein on removal is irrigated with saline solution through a blunt-nosed eye dropper. In 4, the vein has been pushed through the inside of the vitallium tube; the two ends are everted over the ends of the tube and are held in place with one or two ligatures of fine silk. In 5, the distal end of the segment of vein is inserted into the proximal end of the artery and held there by two ligatures of fine silk; all ligatures are placed behind the ridges. In 6, the snug ligature near the end of the vitallium tube, for the apposition of the artery and vein, is being tied. 7 represents the completed operation, showing the bridging of a gap of 2 cm. in the femoral artery. Two tubes were used instead of a single one in all instances.

B, the vein is brought through each vitallium tube and the everted ends held in place by ligatures. The ends of the divided artery are brought over the vitallium tube and held in place by ligatures. This method makes it possible to bridge a gap of any length, the limiting factor being the length of the venous transplant.

Into alternate wounds of all 30 dogs 1.5 Gm. of powdered sulfanilamide was sprinkled at the time of the arterial anastomosis. To 10 of the 20 dogs for which the two tube technic was used 1 Gm. of sulfathiazole was administered orally twice daily (9 a. m. and 5 p. m). To all 10 of the dogs for which the suture technic was used 1 Gm. of sulfathiazole was administered similarly. Therapy with sulfathiazole was begun at the time of the unsterile division of the femoral artery.

RESULTS

There are two yardsticks for the evaluation of the results: (1) the character of the healing of the wounds as observed during the one or two week follow-up and at exploration and (2) the success or failure of the anastomoses to transport blood when examined at the end of the test period. It is worth noting that the latter criterion is a considerably more sensitive measure of minimal bacterial activity than the first. Cultures of material from the wounds were taken to check the above observations.



Fig. 2.—A perfectly healed (4+) wound one week after the performance of the anastomosis

In order to express the data in as quantitative a fashion as possible under the conditions of the experiment, the following scale was used for evaluation of the wounds:

Grade 4 + implies a perfectly healed wound. The edges of the cutaneous incision are firmly joined; the fascia and muscle are relatively dry, are as pale as intact tissue in the same region of the dog and are healing firmly; the anastomosis is well enveloped by cleanly healing tissue (fig. 2).

Grade 3 + implies the same condition as 4 + except that the fascial and muscle layers are slightly edematous and reddened but no free fluid is present.

Grade 2 + signifies that the edges of the cutaneous incision are still adherent but that there are one or more pockets of free nonpurulent fluid deep in the wound. The fascia and muscle are only partially healed.

Grade 1 + implies that the edges of the cutaneous incision are separated; the wound is open to the deep fascia and muscle and some deep collections of seropurulent fluid are present (fig. 3).

Grade 0 signifies that the wound is wide open without any evidence of healing; collections of frank pus are present. The anastomosis may or may not be anatomi-

cally intact. Our observations in the past indicate that in all such wounds thrombosis of the venous segment occurs.

In the 30 animals under discussion no "O" wounds were observed, but they were noted in earlier series when twenty-four hour wounds were treated without débridement.

The following classification of the states of the anastomoses is employed:

- + patent with good blood flow and without any evidence of thrombosis.
- ++ thrombosed completely without any blood flow.
- +++ partially thrombosed but with demonstrable flow of blood through the anastomosis at exploration.

Table 1 shows a comparison of 5 dogs into which sulfanilamide was implanted locally with 5 dogs for which no drug was used. For none of the 10 animals had sulfathiazole been used. Each wound of the treated group healed at least 2+;



Fig. 3.—A wound which is healing poorly (1+) open to the deep fascia with some seropurulent fluid proximally.

TABLE 1.—*Effect of Local Implantation of Sulfanilamide into the Wound When Sulfathiazole Was Not Given Orally*

	Sulfanilamide		No Sulfathiazole	No Sulfanilamide	
	Wound	Anastomosis		Wound	Anastomosis
	3	++	E	1	++
	4	+		4	---
	4	++		2	---
	2	---		2	---
	4	+		3	+
Total	17/20	2/5		12/20	1 5/5
Percentage of normal	85	40		60	30

E, one of the two series of 10 dogs in which nonsuture technic was used
Wound: 4, perfectly healed; 3, well healed except for edema; 2, poor healing muscle and fascia—pockets of clear fluid; 1, edges of skin apart—open to deep fascia with seropurulent fluid; 0, no evidence of healing—frank pus present

Anastomosis: +, patent, with good blood flow and without thrombosis; ++, thrombosed completely; ---, partial thrombosis but with some blood flow

3 out of 5 had wounds graded 4, i. e., perfectly healed, and the average was 3.4 out of a possible 4. On the other hand, in the untreated group 1 dog had a 1 +

wound, only 1 out of 5 had a 4 + wound and the average was 2.4. In other words, healing was 25 per cent less successful than in the treated group.

Secondly, whereas only 1.5 of 5 untreated arterial anastomoses functioned, 2 of 5 of the treated ones were successful. (A partially functioning anastomosis is counted as half an anastomosis.) This difference, although small (10 per cent), is in the same direction as the state of the wounds of the two groups.

TABLE 2.—*Effect of Oral Sulfathiazole on the Wound and Anastomosis in Absence of Local Sulfanilamide*

Sulfathiazole		No Sulfanilamide	No Sulfathiazole	
Wound	Anastomosis		Wound	Anastomosis
<i>A</i>				
4				
4				
4				
1				
1				
<i>D</i>				
3	++		1	++
4	+		4	++
3	+++		2	+++
4	+		2	++
4	+		3	+
Total.....	17/10	3 5/5	12/20	1.5/5
Percentage of normal	88	70	60	30

A, series of 10 dogs in which Carrel suture technic was used. Only the 5 to which no sulfanilamide was given are shown. See table 3; *D*, one of the two series of 10 dogs in which nonsuture technic was used. Only the 5 to which no sulfanilamide was given are shown, was used. See table 3; *E*, one of the two series of 10 dogs in which nonsuture technic was used.

TABLE 3.—*Effect of the Combination of Locally Implanted Sulfanilamide and Orally Administered Sulfathiazole on the Wound and Anastomosis **

Sulfanilamide		Sulfathiazole	No Sulfanilamide	
Wound	Anastomosis		Wound	Anastomosis
<i>A</i>				
4	+		4	+
4	+++		1	+++
3	++		4	+++
4	+		1	++
4	+		4	+++
<i>D</i>				
4	+		3	++
4	+		4	+
4	+		3	+++
4	+		4	+
4	+		4	+
Total.....	39/40	8 5/10	35/40	6/10
Percentage of normal	98	85	88	60

* See tables 1 and 2 for explanation of above data

Table 2 shows the efficacy of orally administered sulfathiazole in a group of animals none of which received sulfanilamide. Two groups of 5 dogs received 1 Gm. of sulfathiazole orally twice daily, and their wounds averaged 3.4 and 3.6 out of a possible 4. In contrast, the untreated group had an average of 2.4 out of a possible 4. In groups *D* and *E*, in which the nonsuture technic was used for all 10 animals, the difference in effective arterial anastomoses was 3.5 out of 5 (70 per cent) in the treated group as compared with 1.5 out of 5 (30 per cent) in the controls. It should be noted that in the sulfathiazole-treated group

3.5 (70 per cent) of the arterial anastomoses functioned, whereas in only 2 (40 per cent) of the group of sulfanilamide-treated dogs were the results satisfactory (table 1).

Table 3 reveals the interesting observation that the combined use of sulfanilamide locally in wounds and sulfathiazole orally brought about the best results of all, i. e., an average of 3.9 of a possible 4. The data in this table show that better results (10 per cent) are obtained in wound healing when one employs local implantation of sulfanilamide in addition to oral administration of sulfathiazole instead of relying solely on the latter. Moreover, 8.5 of 10 (85 per cent) of the arterial anastomoses in the combined treatment group functioned, in contrast to 6 of 10 (60 per cent) in the group for which only orally administered sulfathiazole was employed.

COMMENT

Although the data obtained in these experiments probably are not susceptible of careful statistical analysis, chiefly because of the limited number of experiments, the absolute trend of the findings, i. e., the character of healing the wounds and the patency of the arterial anastomoses, was always in favor of the animals treated with sulfonamide compounds. The interesting observation that there was no significant difference between the effect of sulfathiazole administered orally and that of sulfanilamide implanted locally on the healing of the wound proved that that criterion is not as sensitive as the determination of the patency of the anastomosis. When the latter method of study was used it was discovered that a 30 per cent difference existed in favor of sulfathiazole given by mouth. However, the combined treatment led to a further improvement of 10 per cent in the wound healing (to 98 per cent) and of 15 per cent in the success of the arterial anastomosis (to 85 per cent). It is worth noting that even for the animals given combined treatment, in which the degree of wound healing was 98 per cent, cultures gave positive results in all cases in which they were made (8 of 10) and the organism found was *Staphylococcus aureus* in 6 cases and *Bacillus pyocyaneus* and *Bacillus proteus* in 1 case each.

One possible explanation of the increased effectiveness of sulfathiazole orally over sulfanilamide locally, when the number of patent anastomoses is considered, is that the former drug was administered at the time of the initial unsterile ligation and division of the femoral artery, whereas the sulfanilamide was implanted locally at the time of the second operation, about twenty-four hours later. It is likely that the sulfathiazole would have been less effective if it had been withheld until the second operation. In any case the practical application of these observations to the wounded soldier would be the immediate administration, if possible, of sulfathiazole orally as soon as the injury had occurred and in addition the use of sulfanilamide locally after the wound had been débrided.

A highly significant observation which was made during these studies on delayed anastomoses of blood vessels has to do with the role of débridement in the treatment of wounds. In wounds twenty-four hours old, unless complete débridement was carried out, healing usually was poor (average 1+) and in 13 of 13 cases complete thrombosis had occurred. In this series the 7 wounds into which sulfanilamide had been implanted average 1.5+, in contrast to the 6 wounds without sulfanilamide, in which 0 healing was noted. In none of the foregoing series was sulfathiazole employed. The experimental data just mentioned confirm fully the experience of surgeons of World War I and of the present war that complete débridement is absolutely essential for the adequate healing of a war wound and that sulfonamide compounds locally and orally administered are merely

adjuncts to that treatment. The experimental data show further that the sulfonamide compounds in conjunction with careful débridement are of significant value, whereas when employed without excision of the contaminated and infected tissue they are only of slight aid as far as the wound is concerned.

CONCLUSIONS

During the study of the nonsuture method of bridging a gap in the severed femoral artery of the dog twenty-four hours after its unsterile ligation and division, the following conclusions were drawn concerning the value of sulfanilamide implanted locally and of sulfathiazole administered orally:

1. In the undébrided wound local implantation of sulfanilamide was of little value in regard to the healing of the wound and the patency of the arterial anastomoses.
2. In the carefully débrided wound sulfanilamide applied locally was of significant value in the healing of the wound and in the success of the anastomosis. Sulfathiazole administered orally was slightly more efficacious than sulfanilamide implanted locally.
3. The most satisfactory healing of wounds and the greatest number of successful anastomoses resulted from the combined use of sulfathiazole orally and sulfanilamide locally when careful débridement was done.

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HEMANGIOMA OF THE SYNOVIAL MEMBRANE OF THE KNEE JOINT CURED BY SYNOVECTOMY

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The purpose of this report is to add a case of hemangioma of the knee joint to the few that have already been reported and to reemphasize the differential points and the care which must be observed in distinguishing this condition from hemophilic "arthritis" and other more common swellings of the knee joint.

It is probably safe to state that few hemangiomas of the knee joint are diagnosed immediately, even by experienced physicians. There are several reasons for this lack of accurate diagnoses, in spite of the fact that the clinical picture is rather characteristic, as will be seen later. The disease is rare, the symptoms are relatively nondisabling and nonprogressive and their occurrence is characteristically cyclic. No attempt will be made to review the literature, since Bennett and Cobey¹ have summarized the cases reported in the literature before 1939. At the time of their report 29 authentic cases, including 5 of their own, were on record in the surgical literature. In most of these cases symptoms had been present for years before the patient was seen by the physician who finally made the correct diagnosis. The patients had a history of recurring attacks of pain, swelling and limitation of motion. In no case was hemangioma noted in more than a single joint of each patient. The characteristic recurrent attacks marked by an elastic, doughy swelling which disappeared on elevation of the extremity were present in practically every case. In nearly all cases in which aspiration of the joint was carried out (7 of 8) bloody fluid was obtained.

REPORT OF A CASE

R. N., a boy aged 9 years, had been followed in the outpatient department of the Robert Packer Hospital and the Guthrie Clinic for eight months prior to his admission to the hospital because of a swelling of the left knee. The involved knee had never been particularly tender but had remained consistently swollen. For five years the patient had had intermittent bouts of slight to moderate pain associated with some swelling and a resultant diminution in motion. However, the knee had never been hot to touch, nor had there been any sinus formation. Prior to the patient's admission to the hospital, bloody fluid had been aspirated from the joint on two occasions. The results of several examinations of the blood, including an estimation of the number of platelets, were normal. The coagulation time averaged five minutes and the bleeding time one minute. The sedimentation rate was 10 mm. in sixty minutes.

Roentgen examination of the knee prior to operation (fig. 1) showed multiple small areas of subcortical absorption beneath the articular cortex of the tibia. These areas and the general appearance of the joint in the roentgenogram were suggestive of hemophilic changes. However, the condition of the blood and the fact that no other joints had ever been involved and that there had been no prolonged bleeding after trivial injuries all served to rule out hemophilia.

Inasmuch as the patient remained in good health without involvement of other joints but continued to be bothered by the swelling of the knee, it was thought advisable to perform an exploratory operation, since it was suspected that he might be suffering from a tumor of the synovial membrane.

From the Section on Orthopaedic and Traumatic Surgery, the Guthrie Clinic and the Robert Packer Hospital.

1. Bennett, G. E., and Cobey, M. C. Hemangioma of Joints: Report of Five Cases. *Arch. Surg.* 38:487-500 (March) 1939

The left knee was opened through a 10 inch (25 cm.) lateral parapatellar incision on July 10, 1940, after a 1 inch (2.5 cm.) exploratory incision through the skin of the right thigh had confirmed the fact that the blood clotted normally. When the interior of the joint was exposed, the synovial membrane was found to be greatly hypertrophied, brick red and shaggy. About 60 to 100 cc. of serosanguineous fluid was present. As much of the synovial membrane as possible (estimated at 75 to 85 per cent) was then resected with the scissors. The joint was then closed in layers, the knee slightly but firmly compressed with two elastic bandages and the patient replaced in bed with traction of 7 pounds (3.2 Kg.) applied to the lower part of the leg by means of adhesive tape. The patient's subsequent course was uneventful, and he was discharged from the hospital on the twenty-sixth postoperative day. On discharge, the patient had about two thirds of the normal range of motion and the flexibility of the joint was increasing each day. Weight bearing was satisfactory and without pain.

Microscopic sections prepared from the shaggy, hypertrophied synovial membrane show many hemorrhages, large areas of macrophages packed with hemosiderin granules and universal distribution of small, thin-walled blood vessels (fig. 2).

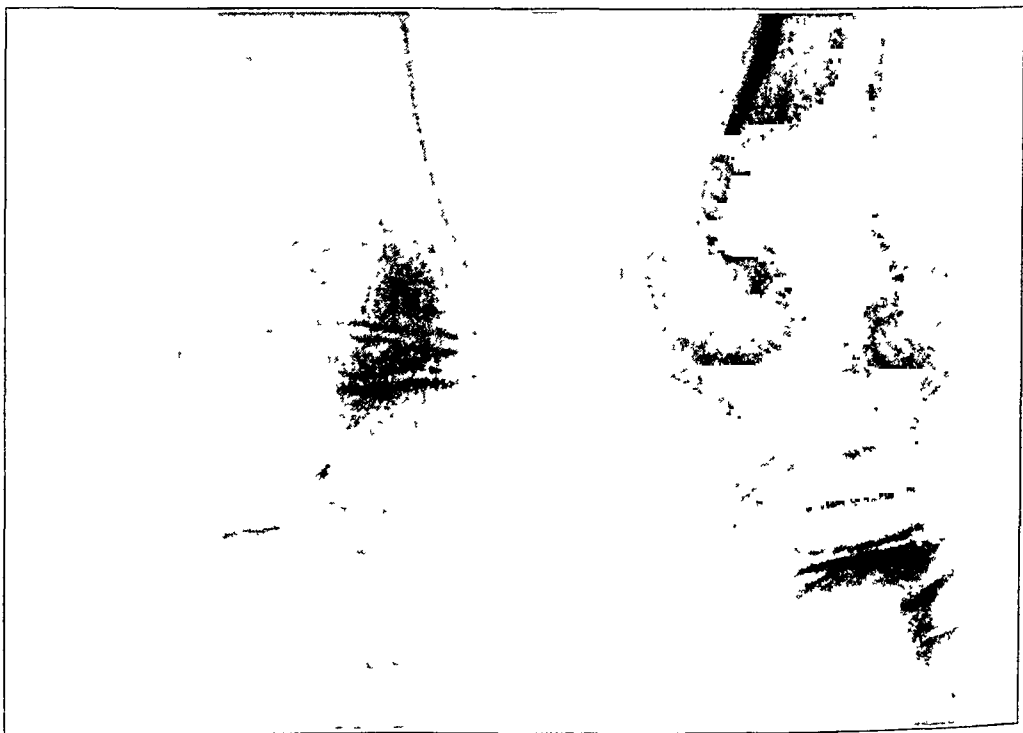


Fig. 1.—Preoperative roentgenograms of the knee which show multiple areas of subcortical demineralization. These roentgenograms are rather similar to those of patients with "hemophilic arthritis."

The patient has been followed for two and one-half years since the operation. There has never been any return of the swelling in the knee, and he has had no pain except that associated with passive and active motion before and immediately after discharge from the hospital.

DIAGNOSIS

All published reports of cases of hemangioma of the knee joint include the same striking symptoms and signs. The swelling of the joint is intermittent and usually of many years' duration, often dating back to early childhood. It is confined to a single joint and has never been of enough moment to detract from the patient's general health. Examination during an acute phase demonstrates that the swelling

disappears to a large extent on elevation or compression of the joint. Motion is limited by the swelling. Roentgenograms may show no abnormalities except the enlargement of the soft tissue shadow, or they may, as in my case, show subcondylar changes rather similar to those encountered after recurrent hemorrhages due to hemophilia. The final diagnosis is usually established at arthrotomy. If the operator opens the joint without interrupting the blood supply of the extremity with a constrictor, he is usually greeted by profuse hemorrhage, which, however,



Fig. 2.—Photomicrograph ($\times 125$) of a section from the synovial and subsynovial tissue removed at operation. The synovial membrane is tremendously thickened, and there are many blood vessels in each synovial villus. The large, deeply stained subsynovial cells are macrophages loaded with hemosiderin. A large blood vessel at the extreme lower left has been sectioned. Elsewhere other blood vessels are seen filled with erythrocytes.

is not difficult to control by packing unless the tumor is one of the rare extensive hemangiomas which invade the adjacent muscle. Fortunately, in the case reported here observations of the joint in the ischemic state were possible. These will be described later

PATHOLOGY

Two gross types of hemangioma are recognized—a diffuse form limited to the synovial membrane and an extensive cavernous form with invasion of the adjacent fascia and muscles. Except for the local extensions of the latter variation of the tumor, the tendency to spread in most cases is limited or nonexistent. In the case reported here, the changes were limited strictly to the synovial membrane and the subsynovial tissues, so that excision of the tumor was synonymous with excision of the synovial lining of the affected joint. The only reported case in which malignant change was observed was that of Downing and Mallory.²

The gross appearance of these tumors in the ischemic state is that of golden yellow, soft, friable synovial membrane. The color is strikingly apparent as soon as the joint is opened and is due to the extensive deposits of hemosiderin in phagocytic cells contained in the connective tissues between the interlacing network of the vessels (fig. 2). Villi are more or less abundant, and in some instances the interior of the joint assumes a shaggy appearance. The microscopic picture of large, irregular blood vessels contained in a stroma of loose connective tissue is identical in all cases. Numerous pigment-containing phagocytic cells are seen in the stroma. The size of the vascular area varies from tumor to tumor, being larger in the exceedingly vascular and invasive tumors and smaller in those restricted to the synovial tissues.

DIFFERENTIAL DIAGNOSIS

Differentiation of this condition is of extreme importance, from the point of view of both prognosis and treatment. A review of the literature and the experience gained from my case demonstrate that a permanent cure is often possible. Inasmuch as the final diagnosis is seldom made until the joint is opened, it would appear logical to excise the tumor, including synovial and subsynovial tissues, by the technic of synovectomy. Unless a constrictor is placed on the extremity above the joint after the diagnosis is confirmed by inspection at operation, or unless this precaution has been taken prior to opening the joint, accurate dissection is not possible because of the profuse hemorrhage. Hemophilic arthritis is definitely ruled out by the fact that the swelling has always been limited to a single joint and the history of subcutaneous hematomas and of bleeding from minor incised wounds is lacking. Finally, the surgeon will find that the patient with hemangioma has a normal number of blood platelets and a normal bleeding and clotting time, whereas in hemophilia the clotting time is greatly prolonged, especially during periods when patients are likely to come under medical observation owing to hemorrhages. It should be again emphasized here that no joint should be opened unless observations on the bleeding and clotting time have ruled out the presence of hemophilia.

The differentiation from chronic pyogenic infection of the knee joint and from tuberculosis of the knee should present few difficulties. The pain and swelling due to hemangioma are usually greater and the course of the disease more continuous. Pyogenic infections and tuberculosis produce characteristic alterations in the roentgenograms, and if no changes are observed in the osseous structures of the knee, aspiration of the joint must be relied on to add confirmatory data. Gross and microscopic observation of the aspirated fluid and cultures for bacteria will aid further in establishing the diagnosis. It should be remembered that the fluid is usually bloody when a hemangioma is present. Routine tuberculin and Wassermann tests may give a clue to tuberculous or syphilitic infections.

2. Downing, J. G., and Mallory, G. K.: Cavernous Hemangioma and Trauma: Report of a Case, *Arch. Dermat. & Syph.* 22:414-422 (Sept.) 1930.

TREATMENT

Within certain limits, it would appear that the earlier in life surgical treatment is undertaken, the quicker will be the alleviation of the patient's symptoms and the establishment of a permanent cure. None of the sclerosing methods usually applied for hemangiomas elsewhere appears to be applicable to hemangioma of the knee joint. Excision by synovectomy appears to be the only satisfactory treatment for the diffuse tumors. However, Bennett and Cobey¹ reported 3 cures with roentgen rays and radium. While complete excision of the synovial membrane is technically impossible, enough of the tumor-bearing area can be removed in the routine synovectomy to effect a cure. Postoperative hemorrhage is never troublesome, since bleeding appears to be well controlled on closure of the joint. The prompt use of a constrictor on establishment of a diagnosis when the joint is opened is recommended, inasmuch as loss of life and/or loss of the extremity occasionally result from either profuse hemorrhage or attempts to control what appears to be a massive hemorrhage.

CONCLUSIONS

A characteristic case of diffuse synovial hemangioma of the knee is reported. Excision of the tumor-bearing synovial membrane was possible and effected a complete cure. The symptoms and signs of hemangioma, as well as the clinical and laboratory data, are characteristic enough so that a definite diagnosis should frequently be made prior to arthrotomy. Hemophilia, of course, should always be kept in mind and ruled out, since it is an absolute contraindication to arthrotomy.

SPONTANEOUS CLOSURE OF AN ARTERIOVENOUS FISTULA

REPORT OF A CASE

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Although in earlier writings¹ it was stated that an arteriovenous aneurysm never heals spontaneously but on the contrary tends to increase in size, it is now a known fact that spontaneous closure of an arteriovenous communication may occur. This statement is supported both by experimental² and by clinical³ evidence. As Holman^{3b} stated: "Nature not infrequently eliminates it by thrombus and fibrous contraction around the abnormal opening." However, we are impressed with the paucity of material written on this particular phenomenon. For this reason we are submitting a detailed report of a case in which spontaneous closure of a femoral arteriovenous fistula occurred.

Reid and McGuire,^{3a} referring to spontaneous closure of arteriovenous fistulas, stated: "In view of these experiences it is probably wise to use every effort to promote spontaneous healing before resorting to surgery." The same authors advised no immediate or early operation unless (1) hemorrhage, (2) diffuse hematoma or infection, (3) rapid cardiac damage and (4) rapidly rising venous pressure are present. He considered it more prudent to delay operation for three to six months after the occurrence of the fistula. There is a greater chance of spontaneous closure if the patient and the part are put at rest.

Holman^{3c} opposed prolonged delay in operating: "If there is early evidence that the heart is increasing in size and that the blood pressure and pulse rate show marked variations on opening and closing a fistula, one may be certain that the lesion will not heal and must be eliminated by operation to avoid further effect upon the heart."

The advantages proclaimed by Reid and McGuire^{3a} of delay in operation, provided that extenuating circumstances previously mentioned do not exist, are the following: (1) hemorrhage is absorbed; (2) tissues are restored to normal, which facilitates dissection of tissue and identification of structures; (3) danger of infection is lessened; (4) collateral circulation develops.

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1. Morel, P.: *Des anévrismes artérioso-veineux du creux poplité*, Thesis, Lyon, no. 61, 1899.

2. Reid, M. R., cited by Holman,^{3b} p. 6. Vignola, cited by Holman,⁵ p. 5.

3. (a) Reid, M. R., and McGuire, J.: *Arteriovenous Aneurysms*, Ann. Surg. **108**:643-693, 1938. (b) Holman, E.: *Arteriovenous Aneurysm*, New York, The Macmillan Company, 1937; (c) Recognition and Treatment of Arteriovenous Communications, Internat. Clin. **4**: 154-167, 1934. (d) Bird, C. E.: Spontaneous Closure of Arteriovenous Fistulas, Surgery **2**:924-929, 1937. (e) Reid, M. R.: Studies in Abnormal Arteriovenous Communications, Acquired and Congenital: I. Report of a Series of Cases, Arch. Surg. **10**:601-638 (March) 1925; II. The Origin and Nature of Arteriovenous Aneurysm, Cirroid Aneurysms and Simple Angiomas, *ibid.* **10**:996-1009 (May) 1925; III. The Effects of Abnormal Arteriovenous Communications on the Heart, Blood Vessels and Other Structures, *ibid.* **11**:25-42 (July) 1925; IV. The Treatment of Abnormal Arteriovenous Communications, *ibid.* **11**:237-253 (Aug.) 1925.

For a complete discussion of the subject of arteriovenous aneurysm the reader is referred to the detailed studies of Reid ⁴ and Holman.⁵

REPORT OF CASE

W. D., a 24 year old Negro, was admitted to Kings County Hospital on Feb. 4, 1941, with a history of having been stabbed in the right groin with a paring knife at about 1 a. m. The blade of the knife broke off in the soft tissues of the thigh, and when it was withdrawn profuse bleeding occurred. He was brought to the hospital by ambulance and was in evident shock due to acute loss of blood. Bleeding was controlled with the aid of a pressure bandage, and shock therapy was instituted.

Physical examination revealed a well developed and well nourished Negro lying restlessly in bed and showing evidence of shock. The temperature was 98.6 F., the pulse rate 84 and the respiratory rate 18. The blood pressure was 70 systolic and 40 diastolic. The significant findings on examination were limited to the right lower extremity. Overlying the right femoral region 1.5 cm. below the middle and inner third of the inguinal ligament there was a stab wound approximately 5 mm. in length transverse to the long axis of the extremity. Below the wound was a hematoma measuring 5 cm. in its greatest diameter. Bleeding was acute and moderately profuse but was controlled by a pressure bandage. Further examination was deferred. A diagnosis of stab wound of the right thigh and shock due to acute loss of blood was made.

Detailed examination seven hours later revealed no evidence of active bleeding, increase in the size of the hematoma or undue tenseness of the surrounding soft tissues. Palpation of the area immediately about the wound revealed a pronounced thrill. On auscultation a loud systolic bruit was heard. The extremity distal to the fistula was warm, and the peripheral pulsations were full and equal to those of the opposite side.

The corrected diagnosis was stab wound of the right thigh and arteriovenous fistula between the right femoral artery and the right femoral vein.

Laboratory Data.—The urine was normal on repeated examination. On February 5 the red blood cell count was 4,100,000 and the hemoglobin content was 11 Gm. per hundred cubic centimeters (71 per cent). The white blood cell count was 10,450, with 52 per cent polymorphonuclear leukocytes, 46 per cent lymphocytes, 1 per cent eosinophil leukocytes and 1 per cent transitional cells. A second examination of the blood on March 4, 1941 revealed a red cell count of 3,580,000 and a hemoglobin content of 13 Gm. per hundred cubic centimeters (82 per cent); a white cell count of 11,500, with 68 per cent polymorphonuclear leukocytes and 32 per cent lymphocytes.

On February 7 the venous pressure in the right antecubital vein at heart level, with the fistula open, was 8 cm. of water. On February 17 it was 9.4 cm. of water, and on February 18, 9.4 cm. of water. An 18 gage needle was used.

On February 7 the pressure in the saphenous vein in the right ankle, with the patient in the horizontal position, was 14.6 cm. of water. The corresponding pressure on the left side was 15 cm. of water. A 20 gage needle was used.

On February 13 the circulation time, after injection of decholin into the left antecubital vein, was eighteen seconds, and on March 3 it was thirteen seconds.

The temperature of the skin (determined with the Taylor dermatherm) showed no abnormal variations.

Electrocardiograms made on March 3 and March 19 were normal. On February 5 roentgen examination of the soft tissues in the region of the stab wound revealed no evidence of any opaque foreign body. A teleroentgenogram revealed a normal cardiac contour. The lungs were normal.

Course in the Hospital.—The patient responded satisfactorily to the usual measures to combat shock. Subsequent treatment was conservative, and the patient was kept in bed until the hematoma was completely absorbed and the wound had healed (twelve days).

Variations in the blood pressure after obliteration of the fistula by digital compression were demonstrated. Prior to closure blood pressure readings for the right arm were 150 systolic and 80 diastolic, and for the left arm, 150 and 80. After closure the readings were 155 and 110 and 160 and 110 respectively. Blood pressure readings in the lower extremities with the fistula open were 160 and 70 for the right leg and 168 and 90 for the left leg, with a demonstrable lowering of the diastolic pressure in the affected extremity.

Similarly, demonstrable differences in the pulse rate were recognized. With the fistula open the rate was 82 beats per minute. On closure of the fistula it dropped to 60.

4. Reid and McGuire ^{3a} Reid.^{3c}

5. Holman.^{3b, c}

The patient's course in the hospital was uneventful, and he was discharged on March 25 to the outpatient department. He was readmitted on May 15 because of a minor infection of the right hand.

Examination at this time revealed the persistence of the previously described arteriovenous fistula in the right femoral region, with no alteration in the local lesion and no evident systemic abnormalities. Studies of blood volume on May 23 revealed a total blood volume of 5,275 cc. and a total plasma volume of 2,345 cc.; the percentage of erythrocytes was 55.4 and that of plasma 45.5. A teleoroentgenogram showed the cardiac contour to be within normal limits. There were no recent pathologic pleural or pulmonic changes present. The Wassermann reaction was negative.

He was discharged May 26 and returned August 6 for elective operation. Examination at this time revealed complete absence of the previously noted thrill and bruit.

COMMENT

The rapidity with which an arteriovenous communication can be produced and clinically recognized is adequately demonstrated in the case presented. The history of a stab wound in the region affected and the profuse but easily controlled bleeding were factors which suggested the possibility of an arteriovenous fistula. The diagnosis was confirmed by the prompt development of a pronounced thrill and bruit which occurred within seven hours after the injury.

Twelve days after the patient's admission to the hospital the hematoma had been completely absorbed. The stab wound was well healed and there was no local tenderness. Despite normal physical activity he had no subjective complaints, and repeated studies failed to reveal any noticeable local or systemic changes as a result of the fistulous communication.

The relative difference in variation between the systolic and the diastolic blood pressure on closure of the fistula is noteworthy but readily explainable. The maintenance of an adequate peripheral resistance in conjunction with the elasticity of the vascular wall are the two basic factors for the development of the diastolic blood pressure. Changes in either of these factors will be productive of alterations in the diastolic pressure, which will be affected in direct proportion to the degree of change produced.

In the presence of an arteriovenous communication the reduction in peripheral resistance is the factor which is altered, with a resultant alteration in the diastolic pressure. The systolic pressure is affected, but to a lesser degree, so that a parallel variation in the systolic and diastolic pressures would not be expected to occur on closure of the fistula. However, cases have been reported⁶ in which the immediate rise in the systolic pressure was as pronounced as that in the diastolic pressure after operative obliteration of the fistula. This rise is transitory and the pressure subsequently falls to a level which approaches or is equal to the preoperative systolic pressure. Conversely the diastolic pressure is stabilized at or falls only slightly below the level that obtained immediately after closure of the fistula.

The increase of 30 mm. of mercury in the diastolic pressure after the fistula was closed led us to believe that a fistulous communication of moderate size was present. Support was given to this belief when it was observed that there was an associated diminution in the pulse rate from 82 beats per minute to 60. These manifestations, associated with the pronounced thrill and bruit which persisted without evident alteration in intensity during an observation period of four months, appeared to indicate that a spontaneous closure would be unlikely. Therefore, surgical intervention was deemed advisable, but when the patient returned for operation at the completion of an arbitrary interval of six months, examination revealed that a spontaneous closure had resulted and that a cure had been effected.

6. Reid and McGuire.^{2a} Holman.^{2b}

Unless there are modifying circumstances, we favor the view expressed by Reid and McGuire,^{3a} that an attempt at closure of the fistula by operation should be delayed for a period of six months. We further believe that if at the end of this time there is evidence of diminution in the size of the communication between artery and vein, as indicated by (1) diminution in intensity of the local thrill and bruit, (2) a distinct lessening of the variation in blood pressure and pulse rate on digital compression of the fistula and (3) absence of local or systemic alterations of function as indicated by clinical and laboratory studies (teleoroentgenograms, studies of blood volume, electrocardiograms, etc.), further observation is justifiable, provided that the patient can be kept under surveillance for a suitable period. If the foregoing signs of improvement have not appeared, or if a further period of observation is not feasible, operation should be performed.

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ROLE OF THE CHEMICAL LABORATORY IN DIAGNOSIS OF NEOPLASTIC DISEASES OF BONE

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Much confusion has existed regarding the significance of changes in the chemical composition of the blood and urine of patients with tumors of bone. This confusion arises mainly from the fact that the chemical changes are nonspecific, several diseases of unrelated cause being capable of causing the same chemical abnormality. If the mechanism of the chemical changes is understood, a consideration of the laboratory data will often establish a diagnosis which could not be made by clinical observation alone. It is the purpose of the present paper to consider the conditions under which this can be done. Only such chemical tests as can be made in the average well equipped hospital laboratory will be considered. For a few patients a diagnosis can be established only by means of the highly specialized procedures employed in metabolism wards, but these are outside the scope of the present paper. Non-neoplastic diseases of the bone will be discussed only so far as is necessary to distinguish between them and tumors of bone.

METABOLISM OF BONE

Before studying the disturbances associated with tumors of bone it is necessary to review the conditions which govern the metabolism of normal bone. These are represented diagrammatically in chart 1. Bones consist principally of tertiary calcium phosphate ($\text{Ca}_3[\text{PO}_4]_2$), but contain also dibasic calcium phosphate (CaHPO_4), calcium carbonate (CaCO_3) and calcium hydroxide ($\text{Ca}[\text{OH}]_2$). The proportions vary with the age and location of the bone, and hence are represented by the general formula $n\text{Ca}_3(\text{PO}_4)_2.\text{CaX}$,¹ which is shown at the right of the diagram. The mineral constituents of bone are embedded in an organic matrix, and the structure contains blood vessels and encloses the marrow cavity. The latter elements are omitted from the diagram for the sake of simplicity, although they are subject to diseases which will be considered later. The constituents of bone are of course derived ultimately from food. Calcium and phosphorus are therefore represented in the column headed "Food" at the left of the diagram. Calcium carbonate is an essential constituent of bone, but, as carbonate deficiencies are unknown, this substance is not included in the diagram. While disease of bone due primarily to protein deficiency has been observed, it usually occurs secondarily to profound disturbances elsewhere in the body and will not be considered here. When the supplies of calcium or phosphorus in the food are inadequate, deficiency diseases of bone, such as rickets and osteomalacia, occur. The same diseases also develop when the diet is adequate but absorption is defective. This may occur in persistent diarrhea because of too rapid passage of the food through the digestive tract, or in sprue, probably owing to loss of calcium as insoluble calcium soaps. A more common cause of faulty absorption is deficiency of vitamin D. While the entire mechanism of the action of vitamin D is not yet known, it appears to be well established that the principal effect of the vitamin

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is to promote absorption of calcium.² Phosphorus is also lost in vitamin D deficiency owing to the formation of insoluble calcium phosphate with the unabsorbed calcium.

After calcium and phosphorus are absorbed from the digestive tract, they are transported in the blood stream to the tissues. In the course of normal or pathologic catabolism the tissues ultimately return these elements to the blood for excretion. The calcium content of erythrocytes is low.³ The total calcium of the blood serum is made up of several fractions,⁴ of which the most important are the ionized and the protein bound.⁵ It is the ionized fraction of the serum calcium which has an important effect on the irritability of muscle. The level of ionized calcium in the serum is controlled by the parathyroids. Serum albumin is more effective than serum globulin in binding calcium.⁶

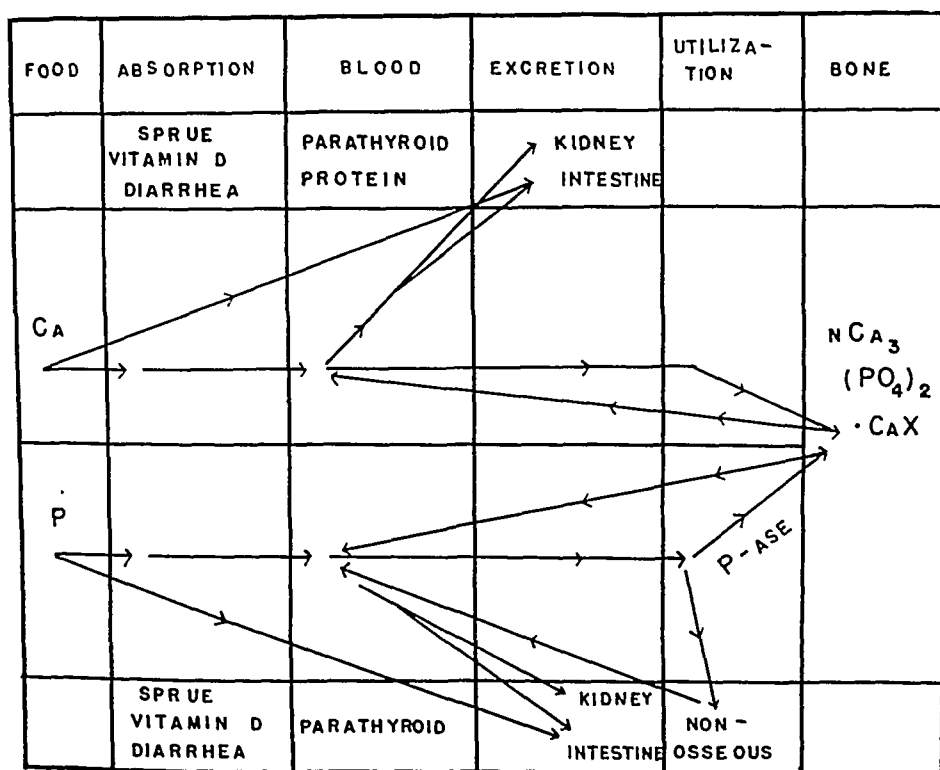


Chart 1.—Conditions which govern the metabolism of normal bone.

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4. Benjamin, H. R., and Hess, A. F.: Forms of Calcium and Inorganic Phosphorus in Human and Animal Sera: Normal, Rachitic, Hypercalcemic, and Other Conditions, *J. Biol. Chem.* **100**:27-55 (March) 1933.

5. McLean, F. C., and Hastings, A. B.: Clinical Estimation and Significance of Calcium-Ion Concentration in Blood, *Am. J. M. Sc.* **189**:601-613 (May) 1935.

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As the major portion of the calcium in the body is in the bones, osseous disease readily causes changes in blood calcium. In contrast to calcium, phosphorus is present in considerable amounts in all the tissues. It occurs in numerous organic compounds in the blood serum. The intermediate product in the transformation of these compounds is inorganic phosphate, and this is the ion which is usually determined in the study of disease of bones. Because this may be derived from nonosseous tissues as well as from bone, the concentration of inorganic phosphate in the serum is not a very sensitive indicator of changes in bone. In particular, ingestion of carbohydrate causes a marked temporary drop in serum inorganic phosphate.⁷

Calcium and phosphorus, whether recently absorbed from the food or derived from tissue catabolism, are carried by the blood to the excretory organs. Most of the calcium and phosphorus found in the feces have never been absorbed, but are residues of food. Small amounts of endogenous calcium and phosphorus do, however, enter the intestinal tract.² The intestine is not a true excretory organ, in the sense that excretion of calcium by this route is not related to the amount of calcium in the blood.⁸ The principal excretory organ for calcium and phosphorus is the kidney. The normal kidney excretes calcium very slowly when the total serum calcium is 7.5 to 9.0 mg. per hundred cubic centimeters, and the rate of excretion rises rapidly when the serum level is greater than 11.5 mg. per hundred cubic centimeters.⁹ It is not yet clear whether the renal threshold for calcium can be influenced directly by vitamin D or parathyroid hormone, but such an effect, if present, is probably small. In general, the urinary excretion of calcium parallels the blood level rather closely. Retention of calcium due to renal insufficiency does not occur unless the damage to the kidney is extremely severe. A primary renal defect has been described¹⁰ which is characterized by inability to form ammonia, with compensatory excessive excretion of calcium and demineralization of bone.

The renal threshold for inorganic phosphate appears to be lowered by vitamin D, dihydrotachysterol and parathyroid, the relative effects of the three substances increasing in the order named.¹¹ In hyperparathyroidism the excretion of phosphorus by the kidney is so great that depletion of the bones results. In renal insufficiency, retention of inorganic phosphate occurs later than that of urea, but the serum inorganic phosphate usually begins to rise when the urea nitrogen content of the blood reaches 35 mg. per hundred cubic centimeters. If the hyperphosphatemia continues for some time, it results in a depression of the serum calcium, which in turn causes the bone disease known as renal rickets.

When adequate amounts of calcium and phosphorus reach the bone, they are deposited as complex calcium phosphates. The mechanism of mineralization has

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been the subject of investigations too extensive to be reviewed in detail here. It is well established, however, that calcifying cartilage can utilize calcium and phosphorus in inorganic solutions *in vitro*.¹² It is further well established that bone elaborates an enzyme, phosphatase, which splits organic phosphorus compounds to supply a local excess of inorganic phosphate.¹³

Bone phosphatase is known as an "alkaline phosphatase" because its activity is at a maximum in alkaline solution. It usually enters the circulation readily and may be demonstrated in the blood serum. While many nonosseous tissues contain alkaline phosphatase, nearly all the alkaline phosphatase in the blood serum is derived from the bones.¹⁴ Alkaline phosphatase is excreted in the bile. The serum alkaline phosphatase is regularly elevated in obstructive jaundice and frequently elevated in hepatic insufficiency. Despite extensive study, it is not yet entirely clear whether this elevation of serum phosphatase is due to simple retention of bone phosphatase, or whether part of the excess phosphatase in the serum originates in the damaged liver. For diagnostic purposes, it is sufficient to remember that elevated values for alkaline phosphatase in the serum of jaundiced patients or of patients with enlarged livers cannot be considered as clearcut evidence of increased activity in the bone.

In subjects with normal livers the alkaline phosphatase of the serum usually parallels that of the bones rather closely. Evidence derived partly from examination of osseous tissue and partly from that of blood serum shows that the phosphatase activity of normal adult bone is low, while that of growing bone is much higher.¹⁵ There is a compensatory increase in alkaline phosphatase when normal bone growth or repair is prevented owing to inadequate supplies of calcium or phosphorus, as in rickets or hyperparathyroidism.¹⁶ Alkaline phosphatase is increased when normal new bone is being formed, as in fractures,¹⁷ or when abnormal new bone is being formed, as in osteitis deformans, osteogenic sarcoma or osteoplastic metastatic

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cancer.¹⁸ Calcification in nonosseous tissues also may be associated with an increase in alkaline phosphatase.¹⁹

While not directly connected with bone metabolism, acid phosphatase is an enzyme whose determination is important in the diagnosis of disease of bone. Many tissues contain small amounts of phosphatases with a maximum activity at p_H 4 to p_H 5, but, so far as is known, the only tissue which contains extremely large amounts of this enzyme is the prostate gland.²⁰ Small amounts of acid phosphatase of unknown origin are present in normal blood serum, but as there is no difference in the serum values for normal males and females, it is evident that prostatic phosphatase does not enter the circulation of healthy men. The acid phosphatase from prostatic cancer which has not metastasized likewise does not enter the circulation. When cancer of the prostate metastasizes either to bone or to soft parts, excess amounts of acid phosphatase can usually, though not always, be demonstrated in the blood serum.²¹

LABORATORY METHODS

In interpreting laboratory data, it is necessary to know how large an experimental error is to be expected, and what conditions are likely to interfere with the validity of the determinations. Hence, a brief discussion of these points is desirable.

Serum Phosphatase.—The determination of phosphatase depends on the measurement of the amount of decomposition which is produced in a phosphate ester under standard conditions. Many methods have been described, but only two are in common use. One, using sodium beta glycerophosphate as a substrate, was developed by Bodansky²² for alkaline phosphatase, and has been modified by Woodard^{15b} for acid phosphatase. The other, using phenyl phosphate as substrate, was developed by King and Armstrong²³ for alkaline phosphatase and adapted for acid phosphatase by Gutman and Gutman.²⁴

18. Gutman, A. B., and Gutman, E. B.: Paget's Disease: Relative Constancy of Serum Phosphatase Levels Over Periods of Two Years, *Proc. Soc. Exper. Biol. & Med.* **33**:150-153 (Oct.) 1935. Woodard, H. Q.; Twombly, G. H., and Coley, B. L.: A Study of the Serum Phosphatase in Bone Diseases, *J. Clin. Investigation* **15**:193-201 (March) 1936. Woodard, H. Q., and Higinbotham, N. L.: The Correlation Between Serum Phosphatase and Roentgenographic Type in Bone Disease, *Am. J. Cancer* **31**:221-237 (Oct.) 1937. Franseen and McLean,^{15a} Woodard,^{15b} Bodansky and Jaffe,^{10b} Gutman, Tyson and Gutman,^{16a} Kay,^{16c}

19. Regen, E. M., and Wilkins, W. E.: Phosphatase in Heterotopic Bone Formation Following Transplantation of Bladder Mucosa, *J. Lab. & Clin. Med.* **20**:250-252 (Dec.) 1934. Wilkins, W. E.; Regen, E. M., and Carpenter, G. K.: Phosphatase Studies on Biopsy Tissue in Progressive Myositis Ossificans, *Am. J. Dis. Child.* **49**:1219-1221 (May) 1935. Woodard,^{15b}

20. Kutscher, W., and Wolbergs, H.: Prostataphosphatase, *Ztschr. f. physiol. Chem.* **236**: 237-240, 1935. Kutscher, W., and Wörner, A.: Prostataphosphatase: II, *ibid.* **239**:109-126, 1936. Gutman, A. B., and Gutman, E. B.: "Acid" Phosphatase and Functional Activity of the Prostate (Man) and Preputial Glands (Rat), *Proc. Soc. Exper. Biol. & Med.* **39**:529-532 (Dec.) 1938.

21. Gutman, A. B., and Gutman, E. B.: An "Acid" Phosphatase Occurring in the Serum of Patients with Metastasizing Carcinoma of the Prostate Gland, *J. Clin. Investigation* **17**: 473-478 (July) 1938. Gutman, A. B.; Gutman, E. B., and Robinson, J. N.: Determination of Serum "Acid" Phosphatase Activity in Differentiating Skeletal Metastases Secondary to Prostatic Carcinoma from Paget's Disease of Bone, *Am. J. Cancer* **38**:103-108 (Jan.) 1940. Herger, C. C., and Sauer, H. R.: Further Observations on Serum Acid Phosphatase Activity in Carcinoma of the Prostate, *Cancer Research* **2**:398-400 (June) 1942.

22. Bodansky, A.: Phosphatase Studies: II. Determination of Serum Phosphatase: Factors Influencing the Accuracy of the Determination, *J. Biol. Chem.* **101**:93-104 (June) 1933.

23. King, E. J., and Armstrong, A. R.: A Convenient Method for Determining Serum and Bile Phosphatase Activity, *Canad. M. A. J.* **31**:376-381 (Oct.) 1934.

24. Gutman, E. B., and Gutman, A. B.: Estimation of "Acid" Phosphatase Activity of Blood Serum, *J. Biol. Chem.* **136**:201-209 (Oct.) 1940.

Determinations of phosphatase are difficult and tedious and require the services of a well trained technician. An error of ± 5 per cent is to be expected under ordinary conditions, and a somewhat larger one when very high values are encountered unexpectedly. Systemic errors as large as 50 per cent may be made when the p_H is not adequately controlled in the determination of alkaline phosphatase. For acid phosphatase some variation in p_H is permissible. For alkaline phosphatase serum may be kept overnight in the ice box, but for acid phosphatase it is essential that the determination be made as promptly as possible.²⁵ Normal values for alkaline phosphatase in adults are 1.5 to 5.0 Bodansky units or 5.0 to 17.5 King-Armstrong units per hundred cubic centimeters of serum. For children the normal value for serum alkaline phosphatase ranges from the upper adult normal value to three times this amount, depending on the rate of growth. Normal values for acid phosphatase in adults are 0 to 1.0 Bodansky units or 0.6 to 3.0 King-Armstrong units per hundred cubic centimeters of serum. Little work has been done on acid phosphatase in children.

Serum Inorganic Phosphate.—The most satisfactory method for determination of serum inorganic phosphate is that described as a part of Bodansky's procedure for phosphatase. No special technical difficulties are ordinarily experienced. Results are commonly reported as milligrams of phosphorus (not phosphate) per hundred cubic centimeters of serum. Normal fasting values for adults are usually between 2.5 and 4.0 mg. per hundred cubic centimeters, although readings as high as 4.5 mg. are found occasionally. The amount of inorganic phosphorus in normal children ranges between 4.0 and 6.0 mg. per hundred cubic centimeters, and may be even higher in infants.^{16a} The amount of inorganic phosphorus in the serum is lowered by the ingestion of carbohydrates.

Total Serum Calcium.—The total calcium of the serum is usually determined by methods based on that of Kramer and Tisdall.²⁶ The method is simple and easy and is usually accurate to 1 per cent. It has the disadvantage that it is possible, through loss of precipitate or inadequate washing of precipitate, to make gross errors without altering the appearance of the material sufficiently to give warning that the results are invalid. For this reason determinations should be done in duplicate whenever possible and should be repeated in critical cases.

Normal values for total serum calcium in the adult have been reported as ranging from 9.0 to 12.0 mg. per hundred cubic centimeters. This wide range may be due in part to the experimental errors mentioned above. In my experience, the great majority of normal adults have serum calcium values between 10.0 and 11.0 mg. per hundred cubic centimeters. Values between 11.0 and 12.0 are occasionally seen in healthy persons who have been exposed to the sun or who have been taking vitamin D. A transitory rise may occur in emotional disturbances accompanied by hyperventilation.²⁷ It is my opinion that, in an adult, a serum calcium lower than 10.0 mg. per hundred cubic centimeters indicates suboptimal nutrition. The total serum calcium of infants and children averages about 1 mg. per hundred cubic centimeters higher than that of adults.

Total Serum Protein.—Numerous methods for the determination of serum protein depending on the decomposition of the protein and the measurement of the resulting ammonia are in common use in clinical laboratories. These methods are usually reliable but time consuming and expensive. A method based on the deter-

25. Woodard, H. Q : Unpublished data.

26. Kramer, B., and Tisdall, F. F.: A Simple Technique for the Determination of Calcium and Magnesium in Small Amounts of Serum, *J. Biol. Chem.* **47**:475-481 (Aug.) 1921

27. Albright, F : Personal communication to the author

mination of the specific gravity of the serum²⁸ has recently come into favor. The method is quick, and is entirely satisfactory, except in serums containing abnormally large amounts of cholesterol. Determinations of albumin-globulin ratio are seldom necessary in the diagnosis of tumors of bone. Normal values for total serum protein usually lie between 6.3 and 8.0 Gm. per hundred cubic centimeters, although slightly lower or higher values are sometimes found.

Various other blood tests, such as those for urea nitrogen and bilirubin, are often necessary to establish the presence or absence of systemic disease which may affect the bones, but the methods for most of these tests are too well established to require comment here.

The only tests of urine which are commonly employed in the diagnosis of tumors of bone are those for Bence Jones protein and for calcium.

The test for Bence Jones protein is a qualitative one, and the result may be obscured by other urinary proteins. Negative findings are not significant, not only for this reason but because many patients with plasma cell myeloma excrete this protein only intermittently or not at all.

Most methods for measuring calcium in the urine depend on precipitation as the oxalate with subsequent titration or ignition and weighing. For accurate balance studies the more tedious gravimetric methods probably are necessary. For such problems as, for instance, distinguishing between nutritional osteoporosis and hyperparathyroidism, the titrimetric method of Shohl and Pedley²⁹ is satisfactory, provided that care is taken to control the alkalinity of the precipitation mixture and to wash the precipitate thoroughly. In many cases in which it is necessary only to establish the order of magnitude of calcium excretion, it is sufficient to test the urine by means of the Sulkowitch reagent.³⁰ This is a semiquantitative test which may be used in following the effect of therapy in cases of parathyroid disturbances in much the same way that the Benedict qualitative test is used in cases of diabetes.⁹

DIFFERENTIAL DIAGNOSIS

While some types of disease of bone may develop in patients of any age, others are much more common in the earlier or in the later years of life. Hence it is convenient to consider first the conditions most often seen in children and young adults, and then to group together those more frequent in middle-aged and elderly patients. The first group includes benign local overgrowths, solitary bone cysts, giant cell tumors, osteogenic sarcoma, endothelioma of bone and reticulum cell sarcoma of bone; the second includes metastatic cancer in bone and plasma cell myeloma. In each group the non-neoplastic diseases most likely to be confused with tumors will also be discussed.

Primary Tumors of Bone.—The majority of primary tumors of bone occur in children or young adults. Hence, in interpreting the chemical findings it is necessary to remember that the value for serum calcium of children is slightly, and that of serum inorganic phosphorus definitely, above the adult normal. The amount of alkaline phosphatase in the serum varies with the rate of growth. A sick child who has stopped growing temporarily may have a value for serum alkaline phos-

28. Weech, A. A.; Reeves, E. B., and Goettsch, E.: The Relationship Between Specific Gravity and Protein Content in Plasma, Serum and Transudate from Dogs, *J. Biol. Chem.* **113**:167-174 (Feb.) 1936.

29. Shohl, A. T., and Pedley, F. G.: A Rapid and Accurate Method for Calcium in Urine, *J. Biol. Chem.* **50**:537-544 (Feb.) 1922.

30. Barney, J. D., and Sulkowitch, H. W.: Progress in the Management of Urinary Calculi, *J. Urol.* **37**:746-762 (June) 1937.

phosphatase within the normal limits for an adult, while an adolescent boy may have five times this amount. The alkaline phosphatase usually reaches the normal adult level about the time the femoral epiphyses close. In these young patients, disease of the liver is uncommon and seldom needs to be considered in interpreting the phosphatase findings.

In the numerous abnormalities, such as chondroma, osteochondroma, osteoma and exostosis, which are characterized by benign localized overgrowth of bony elements, the abnormal tissue contains about the same amount of alkaline phosphatase as normal bone. There are no changes in the amounts of calcium, phosphorus or phosphatase in the serum. If an elevated alkaline phosphatase is encountered in these conditions, the suspicion is warranted that the local process is undergoing malignant change or that disease of bone is present elsewhere in the body.

Bone Cyst.—The type of solitary bone cyst which occurs in the long bones of children causes no change in the chemical composition of the blood. The normal values for calcium and phosphorus and the absence of significant elevation in alkaline phosphatase distinguish these cysts from those caused by hyperparathyroidism.

Giant Cell Tumor.—The material obtained on curettage of benign giant cell tumors usually contains negligible amounts of alkaline phosphatase, and there is no evidence that the bone adjacent to the tumor produces an excess of this enzyme except, perhaps, when fracture has occurred. In tissue from a malignant giant cell tumor there may or may not be considerable amounts of alkaline phosphatase. The value for alkaline serum phosphatase of patients with benign giant cell tumors is usually in the upper normal range; values for serum calcium and phosphorus are normal. In my experience, whenever the value for serum alkaline phosphatase of patients with giant cell tumors has been definitely above normal (6 to 9 Bodansky units) the tumors showed aggressive tendencies or were frankly malignant. The presence of normal amounts of alkaline phosphatase in the serum does not prove that the tumor is benign.

Osteogenic Sarcoma.—Tissue from an osteogenic sarcoma may contain alkaline phosphatase in amounts ranging from those in normal bone (0.1 to 0.5 Bodansky units per gram) to over 100 units per Gm. Two to 10 units is the common range. There is no definite correlation between phosphatase activity and histologic type, although the activity of medullary tumors averages somewhat lower than that of the cortical ones. In general, the greater the formation of new bone, the greater the phosphatase activity, but there are some extremely malignant tumors which contain abundant phosphatase but lay down little new bone. If osteogenic sarcoma is treated by external roentgen irradiation, and if the dose to the tumor (not the skin) equals or exceeds 4,000 r, the phosphatase-producing mechanism is nearly always completely inactivated. Smaller doses result in irregular or incomplete inactivation. Resumption of tumor growth is accompanied by resumption of the production of phosphatase.

The alkaline phosphatase in tissue from an osteogenic sarcoma usually enters the circulation readily and can be measured in the serum. The value may be 10, 20 or even 50 units in excess of the normal for the patient's age. There are, however, some sclerosing osteogenic sarcomas which contain abundant phosphatase but which cause little elevation in the serum readings. Such tumors have a prognosis better than the average. On the other hand, a large amount of alkaline phosphatase in the serum always indicates that the tumor is rather active. If such a tumor has

failed to lay down new bone, the prognosis is especially bad. The values for calcium and phosphorus in the serum of patients with osteogenic sarcoma are normal.

When a patient with osteogenic sarcoma has a high concentration of serum alkaline phosphatase, and the tumor is removed by operation or inactivated by irradiation, the serum phosphatase content falls to normal. Normal levels are reached within two weeks after amputation. If the value for phosphatase does not drop to normal, then residual active disease is present. If the value for the serum alkaline phosphatase of a patient falls to normal and later begins to rise again, metastases are probably developing or an irradiated primary tumor is becoming reactivated. The absence of a rise does not preclude the presence of metastases, since some metastatic deposits, although producing phosphatase, do not allow the enzyme to enter the circulation.

Endothelioma of Bone; Ewing's Tumor.—As this is a tumor of the endothelial, rather than the osseous, elements of bone, the tumor tissue itself does not produce significant amounts of alkaline phosphatase. There is usually a certain amount of reaction in the bone surrounding the tumor, with production of moderately increased amounts of phosphatase. This may lead to an increase in the value for alkaline phosphatase in the serum of 1 to 3 units per hundred cubic centimeters. Such small elevations can be detected with fair certainty in adults, but in children they are masked by the great variability of the normal values. For adults with Ewing's tumor, the values for serum alkaline phosphatase may be used in studying the effect of treatment in exactly the same way that they are for patients with osteogenic sarcoma. The results of such follow-up studies on children are too indefinite to be worth subjecting the young patients to venipuncture. Ewing's tumor causes no changes in the values for serum calcium and phosphorus.

Reticulum Cell Sarcoma of Bone.—In patients with this disease the concentrations of serum calcium and phosphorus are normal and the amount of serum alkaline phosphatase may or may not be slightly elevated. Thus, chemical studies are of no help in distinguishing this tumor from endothelioma or inflammatory disease of bone, both of which it often resembles.

Rickets.—A young patient with a tumor of bone may also have rickets. The high values for serum alkaline phosphatase caused by the latter disease should not be confused with those due to osteogenic sarcoma. In osteogenic sarcoma the values for serum calcium and phosphorus are normal, while in rickets, one or both are low.

Inflammatory Disease of Bone.—This is often confused with various neoplasms of bone and requires separate study. No conspicuous changes in the amounts of serum calcium and phosphorus are found in inflammations of bone. Except in syphilitic disease the serum alkaline phosphatase is either normal or very slightly elevated. The type of productive osteitis which sometimes resembles periosteal osteogenic sarcoma seldom causes any elevation in the amount of serum phosphatase. In such doubtful cases a diagnosis of osteogenic sarcoma is more probable the higher the value for phosphatase, although a normal value does not exclude osteogenic sarcoma. Osteolytic neoplastic diseases of bone cannot be distinguished from destructive nonsyphilitic infections of bone by study of the chemical composition of the blood. In my experience, syphilitic disease of bone is usually associated with a rather high value for serum alkaline phosphatase. It is not known whether this is due to excessive production of alkaline phosphatase by the bone or to inadequate excretion of phosphatase by a damaged liver. The combination of an osteolytic lesion, a positive serologic reaction for syphilis and a value for serum

alkaline phosphatase of 10 to 20 Bodansky units per hundred cubic centimeters makes it extremely probable that the lesion is syphilitic.

Metastatic Cancer in Bone.—When cancer originating in soft tissue metastasizes to bone, the bone may or may not attempt to repair the damage. When little or no attempt at repair is made, little alkaline phosphatase is produced by the bone, and the lesion is predominantly destructive. When an attempt at repair is made, abundant alkaline phosphatase is produced, and the lesion is osteoplastic. The alkaline phosphatase produced by bones which are the site of carcinoma metastases apparently enters the circulation readily, so that there is usually a close correlation between the degree of osteoplasia of the lesion, the amount of alkaline phosphatase found in extracts of the affected bone and the amount of alkaline phosphatase in the serum.

The majority of all metastases to bone are osteolytic, those originating in cancers of the breast, thyroid and kidney being perhaps the most conspicuous. Metastases from cancer of the prostate are almost the only ones which elicit excessive production of alkaline phosphatase and new bone formation with great regularity. In a series of cases from the Memorial Hospital, about 80 per cent of patients with metastases to bone originating in cancers of organs other than the prostate had predominantly osteolytic metastases. In contrast to this, 75 per cent of the metastases to bone from carcinoma of the prostate were almost wholly osteoplastic, and nearly all the remainder showed some degree of formation of new bone. No satisfactory explanation has ever been advanced as to why the bones should differ so much in their response to invasion by different types of cancer. The difference is probably a quantitative rather than a qualitative one, since all gradations in degree of new bone formation are sometimes seen in different bones in the same patient, and since, especially in prostatic carcinoma, individual metastatic areas tend to become more osteoplastic with the passage of time.

With the sole exception of metastatic cancer of the prostate, the site of origin of cancer metastatic to bone cannot be determined by chemical means. Despite this, chemical examination of the blood and urine often gives valuable information as to the existence, extent and activity of metastases to bone.

The typical patient with osteolytic metastases to bone has a slightly elevated value for serum alkaline phosphatase, readings being perhaps 6 to 7 Bodansky units per hundred cubic centimeters. The values for serum calcium and phosphorus tend to be at the upper normal limits or a little above, values in the neighborhood of 12.5 and 4.5 mg. per hundred cubic centimeters respectively being common. The urinary calcium excretion is high even when the patient is on a calcium-poor diet. Even with osteolytic disease the value for serum alkaline phosphatase may rise as high as 20 units, and calcium and phosphorus values of 16.0 and 5.5 mg. respectively or even higher are sometimes seen. Elevations of values for calcium and phosphorus tend to occur together and are less frequent the greater the amount of alkaline phosphatase. It is probable that the elevation of serum calcium and phosphorus is due to a flooding of the circulation with the end products of destruction of bone. Under ordinary circumstances these are excreted by the kidney without significant alteration in the chemical composition of the blood, but when the rate of osteolysis becomes excessive the kidney can no longer keep pace with it, and accumulation in the blood results.

Increases in the amount of inorganic phosphorus and alkaline phosphatase in the serum do not in themselves cause clinical symptoms, although the lesions causing them usually do. Increases in serum calcium, from whatever cause, may be a serious clinical problem. A value of 13.0 mg. per hundred cubic centimeters or

above may cause nausea, lassitude and mental confusion. Such elevations may occur in patients with metastatic cancer in bone even when they are still in sufficiently good general condition to be ambulatory. An erroneous diagnosis of cerebral or gastrointestinal metastases may be made in such circumstances if the serum calcium is not studied.

Patients with osteoplastic metastatic cancer commonly have marked increases in serum alkaline phosphatase, values of 20 to 30 Bodansky units per hundred cubic centimeters being common, and values in excess of 100 units being obtained occasionally. In these patients the calcium and phosphorus of the serum are not increased, and, indeed, the amount of calcium averages somewhat below normal. The urinary excretion of calcium is within normal limits. In these metastases the large amounts of alkaline phosphatase produced by the damaged bone are sufficient to protect it from disintegration. The process is not capable of preserving normal bone structure, but it is able to preserve the constituents of the bone. There is therefore no flooding of the circulation with breakdown products, and the values for serum calcium and phosphorus do not rise.

In actual practice, patients are often encountered whose blood chemical findings present a picture intermediate between those of the two groups described, and some cases of known metastatic cancer to bone show no abnormalities in the chemical composition of the blood. A review of blood chemistry of 250 in our cases with known bone metastases shows that in about three fourths of them an increased amount of calcium, phosphorus or alkaline phosphatase was present. Therefore, although normal results of chemical examination of the blood give no assurance that metastases to bone are absent, they make the presence of such metastases somewhat improbable. An elevated value for serum alkaline phosphatase, on the other hand, nearly always means that disease of either the bones or the liver is present. As the values for alkaline phosphatase will not permit one to distinguish between disease of bone and metastatic or other disease of the liver, it is necessary, before accepting an elevated value for serum alkaline phosphatase as definite evidence that there are metastases to bone, to be sure that there are no signs of disease of the liver.

As has been previously explained, the prostate gland, whether normal, hypertrophied or cancerous, contains large amounts of acid phosphatase. So far as is known at present, this enters the circulation only when a cancerous prostate has ruptured its capsule. An increase in serum acid phosphatase is considered pathognomonic of metastasizing carcinoma of the prostate, and it may occur whether the metastases are to soft parts or to bone. The presence of a normal serum acid phosphatase does not exclude a diagnosis of metastasizing prostatic cancer. In the series from the Memorial Hospital of 61 patients with prostatic cancer with known metastases to bone, 69 per cent had elevations of the value for serum acid phosphatase when first seen; of 37 patients with prostatic cancer with evidence of extension to soft tissues but without known metastases to bone, 41 per cent had elevations. In the majority of cases in which initial readings were normal, the values rose later in the course of the disease. In a few patients, either because the tumor does not produce large quantities of acid phosphatase or because the enzyme does not enter the circulation, the amount of serum acid phosphatase never rises much above the normal limits. We have seen patients in a terminal stage of metastatic prostatic cancer whose serum acid phosphatase was only 2 to 5 Bodansky units per hundred cubic centimeters, and others with readings of 100 units or even, in 1 case, 300 units. For this reason a single determination of serum acid phosphatase does not give a reliable indication of the activity of the disease, but changes in the value for serum acid phosphatase in any one patient give a very sensitive

indication of his clinical progress. In particular, a prompt drop in the value for serum acid phosphatase after the institution of endocrine treatment shows that a favorable clinical response may be anticipated; the failure of the value to drop within one to two weeks shows that the patient is probably refractory to this type of treatment; and a rise in the amount of acid phosphatase in the serum of a patient who has previously shown a satisfactory drop indicates that a clinical relapse may be expected within one to two months.

The great majority of metastases to bone from carcinoma of the prostate show a significant degree of new bone formation. Patients with this condition exhibit an elevation in the value for serum alkaline phosphatase with great regularity, and do not differ in this respect from patients with osteoplastic metastases from cancers originating in other organs. It must be emphasized that in the serum of patients with carcinoma of the prostate metastatic to bone the acid phosphatase is produced by the cancer in the bone or in other regions, while the alkaline phosphatase is produced by the bone around the cancer. The two enzymes may, and frequently do, vary independently. Patients with metastases to bone from carcinoma of the prostate who are receiving endocrine therapy often show a rise in the amount of serum alkaline phosphatase during the first one to two months after the beginning of treatment, followed later by a drop to or toward normal levels. The presence or absence of this rise is not related to the clinical response. Its cause is obscure and cannot be discussed in detail here.

Plasma Cell Myeloma.—This condition, like endothelioma of bone, is a disease in bone but not of bone. Because it occurs in the later age groups and results in destruction of bone, it is often difficult to distinguish from metastatic disease. When active and uncomplicated, it resembles osteolytic metastatic disease in causing slight elevations in the amounts of alkaline phosphatase, phosphorus and calcium in the serum, the reason for these changes being the same in both conditions. The value for serum acid phosphatase tends to be in the upper normal range, but, in our experience, does not rise above normal limits. The distinguishing chemical change in plasma cell myeloma is in the protein constituents of blood and urine. It has been known for many years that about 60 per cent of patients with plasma cell myeloma excrete Bence Jones protein in the urine at some time during their illness. Recently Moore, Kabat and Gutman³¹ have shown that in plasma cell myeloma there may be one or several of a group of abnormal constituents in the globulin fraction of the serum. These may or may not result in a marked increase in the total serum protein. In the average hospital laboratory it is not possible to make protein fractionations such as these, but it is possible and easy to determine total serum protein and urinary Bence Jones protein. If a patient with osteolytic bone disease has a positive test for Bence Jones protein in the urine, or a total serum protein of 8.5 Gm. per hundred cubic centimeters, or both, it is reasonably certain that he has plasma cell myeloma. Negative findings do not exclude this diagnosis. Similar changes are sometimes observed in hepatic disease, leukemia and lymphogranuloma venereum, but these can usually be distinguished clinically from plasma cell myeloma. Severe renal impairment is common in plasma cell myeloma, and the extremely high values for serum inorganic phosphorus sometimes found may be due to retention of phosphorus by the damaged kidney rather than to excessive osteolysis.

There are two types of non-neoplastic disturbances of bone that occur in elderly people, especially women, which may readily be confused with neoplastic disease

31. Moore, D. H.; Kabat, E. A., and Gutman, A. B.: Bence-Jones Proteinemia in Multiple Myeloma, *J. Clin. Investigation* 22:67-75 (Jan.) 1943.

of bone. They are osteomalacia and senile osteoporosis. They are characterized by demineralization, which occurs in the entire skeleton but is most conspicuous in the spine, where it leads to collapse of vertebrae, pain, disability and deformity.

Osteomalacia in the adult is the analogue of rickets in the child and is caused by insufficient intake or faulty absorption of calcium, phosphorus or protein or all three. Patients with this disturbance, although they may be fat, always appear ill nourished. They are notoriously unreliable in their accounts of what they eat, but when a satisfactory history can be obtained, it will show either long-continued poor diet or chronic indigestion. In the serum, the amounts of calcium or phosphorus or protein or all three may be low, according to the nature of the deficiency. The changes are not marked, typical values for calcium being 9.0 to 9.5 mg., for phosphorus, 2.2 to 2.5 mg. and for protein, 5.8 to 6.2 Gm. per hundred cubic centimeters. There is likely to be compensatory hyperparathyroidism, so that in cases in which the main deficiency is in phosphorus and the calcium intake has been adequate, the calcium in the serum may be increased to 12.0 to 12.5 mg. per hundred cubic centimeters. In osteomalacia the reparative mechanism of the bones is normal, so that the amount of alkaline phosphatase in the serum is elevated.

Unfortunately for the problem of differential diagnosis, patients with metastatic disease of bone also are frequently ill nourished, and prolonged observation is often necessary before a multiplicity of diseases can be disentangled. In addition, patients with cancers of the gastrointestinal tract, but without metastases to bone, often have changes in the bones due to faulty absorption of food. It is sometimes helpful in doubtful cases to give large doses of calcium, phosphorus and vitamin D and to follow the Sulkowitch reaction of the urine. If the primary disturbance is calcium deficiency, the excess calcium intake will be stored and the Sulkowitch reaction will not increase. In metastatic cancer of bone the excess calcium cannot be used to repair the defects in the bone and will overflow in the urine.

Senile osteoporosis, a disease described by Albright,³² is due to a defect in the regenerative mechanism of bone, which in turn is probably caused by the endocrine imbalance of later life. Because of the defect, the normal wear and tear on the bones are not repaired, and severe demineralization results. The disease is much more common in women than in men and usually has an insidious onset dating from the menopause. All findings on chemical examination of the blood are normal, and the Sulkowitch reaction corresponds to the calcium intake. The absence of an elevation in the serum alkaline phosphatase serves to distinguish this condition from osteomalacia and from many metastatic cancers in bone. In patients with senile osteoporosis the defective bone cannot utilize the additional building materials made available by large doses of calcium, phosphorus and vitamin D, and the excess calcium spills promptly into the urine, where it can be detected by an increase in the Sulkowitch reaction.

Hyperparathyroidism.—This condition, known variously as von Recklinghausen's disease and osteitis fibrosa cystica generalisata, is due to the increase in the serum calcium and the lowering of the renal threshold for phosphorus which is brought about by excess parathyroid hormone. Both of these conditions result in the loss of large amounts of calcium and phosphorus in the urine, with corresponding depletion of the stores in the bones. In the typical case there are multiple fibrocystic changes in bone, nephrolithiasis and symptoms of hypercalcemia. The amount of calcium in the serum may be anywhere from the upper normal limits

32. Albright, F.; Smith, P. H., and Richardson, A. M.: Postmenopausal Osteoporosis, J. A. M. A. **116**:2465-2474 (May 31) 1941.

to 18 mg. or more per hundred cubic centimeters; the amount of inorganic phosphorus may be from the lower normal limits down to 1.0 mg. per hundred cubic centimeters. The reaction of the urine to the Sulkowitch test parallels the serum calcium and may be extremely pronounced. The value for serum alkaline phosphatase is elevated, the degree of elevation varying with the extent of the damage to the bone, and sometimes reaching 50 Bodansky units per hundred cubic centimeters. The low serum phosphorus will distinguish hyperparathyroidism from osteolytic metastatic cancer in bone. Inasmuch as borderline changes in the serum calcium and phosphorus may occur from emotional or other temporary causes, the determinations should always be made at least twice on blood samples drawn on different days.

While the typical patient with hyperparathyroidism shows a high value for serum calcium, a low value for serum inorganic phosphorus, a high value for serum alkaline phosphatase and a pronounced reaction to the Sulkowitch test, the disease exhibits many confusing variations. Thus, a patient with acute hyperparathyroidism of recent onset who is on a high calcium diet may have a dangerous hypercalcemia and stag horn calculi in the kidneys but only mild demineralization of bone, the high calcium diet having protected the bone from destruction. On the other hand, a patient with mild disease of many years' standing who is on a low calcium diet may have such extreme demineralization that the amount of calcium in the serum can no longer rise, and may even be below normal. Another complication may be found in cases in which stones have been present in the kidney long enough to cause severe renal insufficiency. In these, the damaged kidney can no longer maintain a low threshold for phosphorus, and the value for serum phosphorus, instead of being below normal, may be high. In these patients, other signs of renal disease are readily discovered. Thus, while in typical cases hyperparathyroidism may easily be distinguished by the chemical composition of the blood from metastatic cancer in bone, this disease is often accompanied by secondary changes which must be taken into account before a differential diagnosis can be arrived at.

It is well known that immediately after a parathyroid adenoma which has been causing hyperparathyroidism has been removed, the patient often goes into acute hypoparathyroid crisis. This is characterized by a rise in serum inorganic phosphorus and drop in serum calcium, the latter condition leading to tetany. Since a satisfactory determination of serum calcium cannot be made in less than six to eight hours after the blood is drawn, there may be a dangerous delay in the institution of therapy. It is, therefore, well to remember that a sudden rise in serum inorganic phosphorus is as reliable an indication of hypoparathyroidism as a sudden drop in serum calcium and that determinations of serum phosphorus can be made in less than an hour.

Osteitis Deformans; Paget's Disease of Bone.—The roentgenographic picture in this condition often resembles that in carcinoma of the prostate metastatic to bone. In osteitis deformans, the amounts of calcium, phosphorus and acid phosphatase in the serum are normal, and the value for alkaline phosphatase is greatly elevated, sometimes reaching 200 Bodansky units per hundred cubic centimeters, although values of 20 to 40 units are more common. If the amount of both the acid and the alkaline phosphatase in the patient's serum is above normal, he has metastasizing carcinoma of the prostate. He may also have osteitis deformans, but this is not likely. If he has a very high value for serum alkaline phosphatase and a normal value for serum acid phosphatase, he probably has osteitis deformans, but this is not

certain, since some patients with metastasizing carcinoma of the prostate have no elevation in acid phosphatase. Nor will a very high alkaline phosphatase in a female patient in itself establish a diagnosis of osteitis deformans, since any condition in which large amounts of new bone are being formed will raise the alkaline phosphatase of the serum. Nevertheless, the amount of alkaline phosphatase in osteitis deformans is often so high as to leave little doubt of the diagnosis, especially for a patient in good general condition and without severe symptoms.

Many observers have found that the serum alkaline phosphatase of patients with osteitis deformans shows little variation over a period of years. My associates

Summary of Chemical Findings in Neoplastic Diseases of Bone

Disease	Serum Acid Phos- phatase	Serum Alkaline Phos- phatase	Serum Inor- ganic Phos- phorus	Total Serum Calcium	Sulko- witch Reaction of Urine	Urine, Bence Jones Protein	Total Serum Protein
Chondroma, osteochondroma, osteoma, exostosis	Normal	Normal	Normal
Solitary bone cyst.....	Normal	Normal	Normal
Giant cell tumor.....	Normal	Normal or slightly raised	Normal	Normal
Osteogenic sarcoma.....	Normal	Usually high	Normal	Normal
Endothelioma of bone.....	Normal or slightly raised	Normal	Normal
Reticulum cell lymphosarcoma of bone	Normal or slightly raised	Normal	Normal
Rickets.....	High	Normal or low	Normal or low
Inflammatory disease of bone...	Usually normal	Normal	Normal
Osteolytic metastatic disease....	Normal	Normal or moder- ately raised	Normal or high	Normal or high	Pro- nounced	Negative	Normal
Osteoplastic metastatic not from prostate	Normal	High	Normal	Normal	Normal	Negative	Normal
Carcinoma prostate metastatic to bone	High in 70% of cases	High	Normal	Normal	Normal	Negative	Normal
Plasma cell myeloma.....	Normal	Normal or slightly raised	Normal or high	Normal or high	Positive in 60% of cases	Normal to very high
Osteomalacia.....	Normal	Moder- ately raised	Normal or low	Usually low	Usually slight	Normal or low
Senile osteoporosis.....	Normal	Normal	Normal	Normal	Normal	Normal
Hyperparathyroidism.....	High	Low	High	Pro- nounced
Osteitis deformans.....	Normal	High	Normal	Normal	Normal	Normal

and I have confirmed this observation in general, but have found occasional exceptions. A few patients who had shown constant values for serum alkaline phosphatase for several years showed a sudden rise to double the usual value. Simultaneously there was an increase in symptoms, and in 1 patient an osteogenic sarcoma developed. The average osteogenic sarcoma does not contain more phosphatase per gram of tissue than does the bone of osteitis deformans. Hence, the rise in serum phosphatase in this case was probably not due to the presence of the sarcoma, but was an indication of an increase in activity of bone, which in turn led to malignant change. It has also been found that, just as an acute illness

may stop normal growth of bone in a child, so systemic disease may reduce activity of bone in osteitis deformans, with an accompanying drop in serum alkaline phosphatase in both cases.

SUMMARY

The accompanying table summarizes the chemical findings in typical cases of various neoplastic diseases of bone and in the non-neoplastic diseases most likely to be confused with them. The first eight entries show conditions most commonly found in children and young adults; the remainder of the table shows those most frequently found in older patients. Where a space is left blank, detailed studies are lacking, but abnormal values have not been reported.

The members of the Bone, Urological and Breast Departments of the Memorial Hospital for the Treatment of Cancer and Allied Diseases furnished the clinical material presented in this paper.

The Memorial Hospital for the Treatment of Cancer and Allied Diseases.

PROGRESS IN ORTHOPEDIC SURGERY FOR 1942

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE AMERICAN
ACADEMY OF ORTHOPAEDIC SURGEONS

V. INFANTILE PARALYSIS

PREPARED BY LENOX D. BAKER, M.D., AND HOWARD SCHAUBEL, M.D., DURHAM, N. C.

(Continued from page 318)

Introduction.—During these times of war and in the presence of much argument in the lay press as to the therapy of infantile paralysis, it is encouraging to review the excellent studies which have been reported during 1942 on the causation, epidemiology, means of transmission and true pathogenesis of poliomyelitis. Certainly the workers behind the scenes are to be commended for their untiring efforts to establish means of controlling the disease.

Causation, Transmission and Epidemiology.—McClure and Langmuir¹⁰² report the recovery of poliomyelitis virus from the feces of 4 of 5 patients with acute poliomyelitis in a rural community in the state of New York and from the feces of 20 of 27 contacts of the patients. They did not recover the virus from the feces of 4 persons who had histories of having had poliomyelitis in the past or from the feces of 4 persons in the same community who had no contact with the patients. Trask and Paul,¹⁰³ continuing their original work, collected samples of unchlorinated sewage from New Haven, Conn., and New York monthly over a period of fifteen months from April 1940 through June 1941. Of forty-five monthly tests for poliomyelitis virus, thirty-six were completed, and thirty-five of these gave negative results. The sample that contained the virus was collected on Sept. 19, 1940, and the test monkey became ill with poliomyelitis on October 1. It is of interest that during the period the tests were made there were remarkably few cases of infantile paralysis in New York and New Haven. The authors feel that the result of their investigation and its relation to cases of poliomyelitis reported adds little to the knowledge of the pathogenesis of poliomyelitis. Their study is of value in that they were unable to detect the virus of poliomyelitis in sewage during nonepidemic periods, and it is likely that the periodic sampling of sewage for pathogenic virus or bacteria may be a method of epidemiologic importance. Howitt, Buss and Shaffrath¹⁰⁴ made examinations of stools in Kern County, Calif., where poliomyelitis has occurred each year in the same geographic area since 1938. Examination of specimens collected in 1941 from 11 patients with onset of the disease in 1939 and from 8 with onset of the disease in 1940 did not show the presence of the poliomyelitis virus.

However, stools from 4 (28.5 per cent) of the 14 patients for whom a diagnosis of poliomyelitis was made in 1941 yielded the virus. Three of these patients lived under rural or semirural conditions, and the active agent was recovered from the privies of 2 families. The virus was obtained from the feces of 1 patient in five,

102. McClure, G. Y., and Langmuir, A. D.: Search for Carriers in Outbreak of Acute Anterior Poliomyelitis in Rural Community: Incidence of Virus in Feces, *Am. J. Hyg.* **35**: 285-291 (March) 1942.

103. Trask, J. D., and Paul, J. R.: Periodic Examination of Sewage for Virus of Poliomyelitis, *J. Exper. Med.* **75**:1-6 (Jan.) 1942.

104. Howitt, B. F.; Buss, W. C., and Shaffrath, M. D.: Acute Anterior Poliomyelitis in Kern County, California, *Am. J. Dis. Child.* **64**:631-648 (Oct.) 1942.

fifteen and twenty-four days but not in thirty-nine or seventy-three days after the onset of the disease and from other patients in five, fourteen and fifty days after the appearance of the first symptom. Undiluted specimens of stools kept for four months at -70°C . contained active virus, while the virus remained viable in frozen untreated feces for periods varying from seven days to five and one-half weeks before being inoculated into monkeys. The feces of 7 (22.4 per cent) of 31 healthy contacts of patients with poliomyelitis gave evidence of the virus when inoculated into monkeys. All contacts except 1 were children. No virus was obtained from nine samples of sewage, from bird and chicken feces or from a limited number of house flies collected during this interepidemic period.

Toomey, Takacs and Tischer¹⁰⁵ set fly traps near the mouth of a brook that emptied raw sewage into Lake Erie. Excrement was plainly visible on the top of the water. This brook drained parts of the northeastern section of the city of Cleveland, where the epidemic first appeared this year—an area in which a large number of cases were found. A large yield of flies was obtained, mostly large blow flies, with only an occasional small house fly and a few wasps and moths. About 2,000 etherized flies were put in a glass bead grinder and prepared for injection into monkeys. Two animals were used, and the disease developed in both. A 10 per cent suspension of the cord of the first animal killed was injected into a third monkey, and the disease was produced. In spite of these results Toomey and his associates feel that the facts were of slight epidemiologic importance, because: (1) in twenty experiments over a ten year period the virus was not obtained from house flies consistently during either epidemic or nonepidemic years; (2) the disease did not always occur in crowded communities infested with flies, but appeared more often in clean surroundings devoid of flies; (3) the peak of the disease and that of the fly population did not correspond.

Lumsden¹⁰⁶ in an epidemiologic study of poliomyelitis in Mississippi noticed that over two thirds of the afflicted persons lived in open country homes. A seasonal prevalence was as follows: 1 case in February, 1 in March, 3 in May, 16 in June, 28 in July, 29 in August, 13 in September and 8 in October. Lumsden concludes that poliomyelitis is spread not by personal contact but by unknown factors. The picture as a whole suggests infection by place rather than by person. His community studies substantiate his conclusions.

Hershey¹⁰⁷ reports public health measures used during the summer of 1941 in Okanagan Valley, British Columbia. Early in the summer prepared circulars stressing the importance of early diagnosis and outlining diagnostic points and methods of prevention and control were supplied to the physicians of the province. Attempts to control the spread of this disease after it had broken out in the district depended almost entirely on rigorous control of sanitation and institution of quarantine for a period of six weeks for all persons known to be contacts. It was concluded that half measures were useless in attempting to control the spread of acute anterior poliomyelitis, but by rigorous efforts the 1941 epidemic was broken off at a time when further cases might have been expected in a district that had suffered heavily in previous outbreaks.

105. Toomey, J. A.; Takacs, W. S., and Tischer, L. A.: Poliomyelitis Virus from Flies, *Proc. Soc. Exper. Biol. & Med.* **48**:637-639 (Dec.) 1941.

106. Lumsden, L. L.: Epidemiological Study of Poliomyelitis in Mississippi in 1941, *Pub. Health Rep.* **57**:729-753 (May 15) 1942.

107. Hershey, J. M.: Outbreak of Acute Anterior Poliomyelitis in Okanagan Valley, British Columbia, *Canad. Pub. Health J.* **33**:452-460 (Sept.) 1942.

Dauer¹⁰⁸ reports the prevalence of poliomyelitis in the United States in 1941. In 1940 the disease occurred in epidemic form in several large areas in the north central and northwest sections of the country, with rather high rates in West Virginia, Kansas, Minnesota and Michigan. In 1941 poliomyelitis was most prevalent in the eastern, south central and south Atlantic states. Four southern states, Alabama, Florida, Georgia and Tennessee, accounted for approximately one fourth of all of the cases reported in the entire country. In the middle Atlantic states and in Minnesota the incidence of the disease was slightly higher than for the country as a whole. Several investigators studying feces of flies reported recovery of poliomyelitis virus from the flies caught in areas where the disease was prevalent in the summer of 1941.

Susceptibility and Immunity.—Aycock¹⁰⁹ reviews several sets of observations, all of which, under the concept outlined, are consistent with hereditary susceptibility as a factor which determines the occurrence of paralysis in a selected few of the many exposed to the virus. The intensity with which the hereditary susceptibility is exhibited in the distribution of the disease, as indicated by these studies, clearly is not sufficient to afford any basis in itself for controlled measures, but rather forms a background for a study of the nature of individual susceptibility to paralysis and suggests that the search for predisposing causes should include conditions inherent in the constitutional makeup of the patient.

Howe and Bodian¹¹⁰ point out that it is generally conceded that a relatively substantial and lasting immunity to poliomyelitis is conferred through the invasion of the nervous system by active virus. However, well authenticated second attacks of the disease do occur both in human beings and in experimental animals. The type of immunity which occurs is thought to be a local one, and such immunity of the nervous system may be further restricted to include only portions of it. In 40 rhesus monkeys, intracerebral, intraocular, intracutaneous, intraperitoneal, intraspinal and intraneural inoculations of poliomyelitis virus produced no lesions in the olfactory bulb despite the fact that the animals contracted paralysis. Two monkeys, convalescent from an intracutaneous and intracerebral inoculation respectively, had further paralysis after intranasal inoculation of heterologous virus. A third animal, convalescent from an intranasal inoculation, showed extension of the lesion after intranasal and intraocular inoculation with heterologous virus. Two animals in which the spinal cord had been transected and in which an attack of poliomyelitis was limited to an isolated segment of cord contracted typical paralysis in previously uninvaded portions of the central nervous system after intranasal inoculation of homologous virus. Four of 6 convalescent monkeys showed extension of lesions but no clinical signs after inoculation of homologous virus through a previously uninvaded portal. Four animals convalescent from a unilateral intranasal inoculation showed evidence of new invasion in the opposite olfactory bulb but no extension of paralysis after a second inoculation of homologous virus into the nostril. Two animals had second attacks after a heterologous second inoculation. The intranasal portal was used for both exposures. They conclude that in the rhesus monkey a second attack of poliomyelitis, whether paralytic or not, seems to depend on the strains of virus used and the degree to which the virus is disseminated through

108. Dauer, C. C.: Prevalence of Poliomyelitis in United States in 1941, *Pub. Health Rep.* **57**:710-716 (May 8) 1942.

109. Aycock, W. L.: Familial Aggregation in Poliomyelitis, *Am. J. M. Sc.* **203**:452-465 (March) 1942.

110. Howe, H. A., and Bodian, D.: Relation of Fiber Pathways to Local Immunity in Experimental Poliomyelitis, *Tr. Am. Neurol. A.* **67**:122-124, 1941.

the neuraxis during the first exposure. They feel that the experimental data emphasize the difficulty of neutralizing rhesus monkeys for experiments seeking to clear mechanisms of immunity in man and suggest that human immunity to poliomyelitis does not result from immunization of the central nervous system but rather is a result of some process which prevents infective quantities of active virus from reaching nerve tissue (portal immunity).

Aycock¹¹¹ made neutralization test studies using four strains of poliomyelitis virus. He showed that monkeys which had recovered from attacks produced by the H virus regularly neutralized this virus but failed to neutralize the Aycock or the Trask virus. Monkeys that have recovered from attacks produced by both the Aycock and the H strain neutralize both these strains of virus as well as the J strain. Of 4 animals, 1 that had recovered from an attack produced by the H virus and 3 that had recovered from attacks produced by the H virus and the Aycock virus, all failed to neutralize the Trask virus. These tests clearly reveal immunologic differences between these strains of virus and in turn serve to explain the failure of convalescent patients in a school outbreak to neutralize the old laboratory Aycock strain of virus. It is suggested that the momentary immunity status of the patients is represented by the presence of neutralizing antibody to strains to which they have been exposed previously and that the end point of immunity (adult) is represented by the presence of neutralizing antibody to a number of strains.

Pathology.—Sabin¹¹² deals with three major questions: 1. What are the essential lesions of poliomyelitis, and where are they located? 2. How extensive must these lesions be to produce paralytic disease, and what is the basis for the transitory character of some of the paralysis? 3. What determines the special localization and distribution of the lesions? These questions are answered as follows: 1. The upper motor neurons concerned in initiating voluntary movement may be significantly and predominantly affected. The essential lesions are characterized by perivascular cupping, neuronophagia and focal mesodermal-glial infiltrations in all layers. 2. Edema and its disappearance do not cause transitory paralysis. Instead, in cases of transitory paralysis the segmental distribution of the lesions is spotty and does not affect the major innervation of a given muscle; thus a muscle may have enough innervation to regain normal strength. The lesions must be extensive to cause complete paralysis. 3. The virus is found in certain regions of the nervous system and in the gastrointestinal tract. The part of the central nervous system first to be attacked by the virus is determined by the neural connections from the peripheral tissue from which the virus invades, and its subsequent spread within the nervous system is dependent on the central connections of the neurons in which the greatest proliferation of virus occurred. Sabin concludes that a thorough reinvestigation of the pathologic physiology of poliomyelitis is needed.

Schwartz and Bouman,¹¹³ aided by a grant from the National Foundation for Infantile Paralysis, made an interesting study to determine if spasticity existed in the early stages of poliomyelitis. They made oscillographic records of muscle action currents through a four stage amplifier. Their studies were applied to 7

111. Aycock, W. L.: Immunity to Poliomyelitis: Heterologous Strains and Discrepant Neutralization Tests, *Am. J. M. Sc.* **204**:455-467 (Sept.) 1942.

112. Sabin, A. B.: Pathology and Pathogenesis of Human Poliomyelitis, *J. A. M. A.* **120**: 506-511 (Oct. 17) 1942.

113. Schwartz, R. P., and Bouman, H. D.: Muscle Spasm in Acute Stage of Infantile Paralysis as Indicated by Recorded Action Current Potentials, *J. A. M. A.* **119**:923-926 (July 18) 1942.

patients with infantile paralysis, 3 with spastic paralysis and 3 normal subjects for control. They feel that their results justify the following conclusions: 1. In infantile paralysis spasticity of the muscles exists not only in antagonists of the weakened muscles but in the weakened muscles themselves and in muscles in parts of the body in which clinical symptoms of the disease are not evident. 2. The spasticity is of a reflex nature and is not present in the completely paralyzed muscles. 3. The spasticity can be stronger than the voluntary contraction which the muscle is able to perform, as adjudged by action current. 4. When the strength of the voluntary contraction increases through treatment, the spasticity decreases. Schwartz and Bouman cannot say whether the spasticity is actually responsible for weakening of the muscles or whether it is a phenomenon which is merely another consequence of the disease.

Chown,¹¹⁴ in discussing the feasibility of some of the present concepts of treating the disease, points out that poliomyelitis is an encephalopoliomyelitis and ganglionitis which gives a background not for a single simple picture of flaccid paralysis but for diverse symptoms and signs, such as incoordination, tremor, variations in clonus and autonomic anomalies, as well as transitory signs and symptoms, temporary paralysis and what is referred to as "mental alienation." Chown points out that one cannot use the known pathologic picture of the disease to justify a refusal to reexamine the clinical picture and states that the whole disease is in need of reassessment. Hipps¹¹⁵ made a study of the pathologic changes in muscles paralyzed by poliomyelitis. A study was made on muscles the strength of which was known and which had been paralyzed for two years or more. The three most interesting and common microscopic observations were: (1) increased interfascicular fibrosis, (2) atrophy and disintegration and (3) large round cells found in muscle bundles containing atrophic cells. A general comparison of the sections from all of the 94 examined muscles revealed the following significant facts: 1. The age of the patient seems to have no bearing on the microscopic picture of any muscle. 2. The muscles showing fatty replacement changes are uniformly weaker muscles than those showing fibrous replacement changes. 3. Fifty per cent of the muscles examined showed cellular hypertrophy in involved bundles. 4. Sections showing cellular hypertrophy almost invariably were from muscles graded "poor" or better, there being only 1 graded "trace" and none graded "zero."

No newly formed or regenerated muscle cells were found in any section, and the author concludes that a gain in strength by partially paralyzed poliomyelitic muscle does not occur through the formation of new muscle fibers but through an overdevelopment or hypertrophy of remaining undamaged cells. He points out that pathologic changes occurring in muscle following acute anterior poliomyelitis are brought on in two ways, primarily through denervation and secondarily from abnormal variations of tension in the muscle. The cellular changes from denervation begin with atrophy and progress to degeneration, disintegration and changes due to replacement. These pathologic changes occur in muscle cells in exactly the same way when they are due to secondary factors. Too much tension or overstretching results in minute tears, zonal degeneration and subsequent fibrosis. The changes produced are identical with those produced by denervation, and the rate of change is nearly as fast. These secondary abnormalities may cause just as much weakness in a muscle as the changes due to primary denervation.

114. Chown, B.: Newer Knowledge of Pathology of Poliomyelitis, *Canad. Pub. Health J.* **33**:276-277 (June) 1942.

115. Hipps, H. E.: Clinical Significance of Certain Microscopic Changes in Muscles of Anterior Poliomyelitis, *J. Bone & Joint Surg.* **24**:68-80 (Jan.) 1942.

Examination.—Eyre-Brook¹¹⁶ points out the importance of taking more than one specimen of cerebrospinal fluid in a case of suspected poliomyelitis and calls attention to the necessity for proper interpretation of the observations in the light of the changing picture presented by the spinal fluid. Spinal fluid in acute poliomyelitis shows an early rise in cell count and a late rise in protein content. A single specimen taken at the end of two weeks may give a normal picture, since the increase in the number of cells is almost ended and the increase in the amount of protein may hardly have begun. Studies of spinal fluid from 7 patients are discussed, and the results confirm the author's opinion of the value of repeated lumbar punctures in cases of suspected poliomyelitis.

Carroll¹¹⁷ made an after-effects survey for poliomyelitis in patients treated at the Orthopaedic Hospital in Los Angeles. His series included patients treated during a period of twenty years. There were over 1,700 patients, and more than 1,500 had recorded checks of the muscles to determine the rate and amount of improvement in muscular strength. It was concluded that when paralysis was not complete an increase in muscular strength was made in the majority of cases. Approximately two thirds of the increase was made during the first six to eight months after onset of the paralysis.

Mayer and Greenberg¹¹⁸ describe a gravity scale and a swivel table which they have used to evaluate the power of the muscles of the trunk. They hope that the scale and table can be used to learn more about the cause of postural defects, painful backs and scoliosis as well as residual paralysis.

De Sanctis and Green¹¹⁹ report 2 cases of acute infectious polyneuritis as diagnostic problems during a poliomyelitis epidemic. They point out that clinically the two diseases appear similar but when examined more minutely they do differ. The history of both conditions is usually that of a slow progression of symptoms and signs, although the onset of acute infectious polyneuritis occasionally may be sudden and overwhelming. Both diseases cause hyperesthesia, but in poliomyelitis this is really pain in the muscles brought on by activation and deep pressure. In infectious polyneuritis the patient in addition to having pain in the muscles is hyperesthetic to superficial touch. Both diseases may cause nuchal rigidity and tenderness of the muscles of the back, although these complaints are rare in cases of infectious polyneuritis. The progress of the paralysis is ascending in both conditions, but they differ in their types of involvement. The paralysis of polyneuritis is usually symmetric and bilateral and involves the proximal muscles of the extremities more severely than the distal ones. Involvement of the cranial nerves is limited mainly to the seventh nerve. Paralysis in poliomyelitis is usually segmental and is not necessarily symmetric or bilateral but often unilateral and irregular in distribution. Involvement of cranial nerves may be multiple. The writers point out the importance of differential diagnosis because of the favorable prognosis in infectious polyneuritis for recovery from paralysis, and they emphasize changes in the spinal fluid as a key to the diagnosis. Polyneuritis causes an elevated protein content without a change in cell count, and in anterior poliomyelitis there are both a cellular increase, which very early is polymorpho-

116. Eyre-Brook, A. L.: Cerebrospinal Fluid in Acute Anterior Poliomyelitis, *Brit. M. J.* **1**:758-759 (June 20) 1942.

117. Carroll, R. L.: Rate and Amount of Improvement in Muscle Strength Following Infantile Paralysis, *Physiotherapy Rev.* **22**:243-257 (Sept.-Oct.) 1942.

118. Mayer, L., and Greenberg, B. B.: Measurements of Strength of Trunk Muscles. *J. Bone & Joint Surg.* **24**:842-856 (Oct.) 1942.

119. De Sanctis, A. G., and Green, M.: Acute Infectious Polyneuritis: Diagnostic Problem During Poliomyelitis Epidemic, *J. A. M. A.* **118**:1445-1447 (April 25) 1942.

nuclear and a little later lymphocytic, and a moderate rise in the value for protein. De Sanctis and Green maintain that this difference in the spinal fluid confirms the diagnosis.

[Ed. NOTE.—The authors' favorable prognosis for acute infectious polyneuritis is not altogether in agreement with previous reports in the literature and their interpretations of the spinal fluid changes are not altogether in agreement with the report by Eyre-Brook.¹¹⁶]

Hansson,¹²⁰ in a report on electromyographic investigation of muscles in anterior poliomyelitis, describes an electromyograph for making oscillographic readings of muscular contractures. He found it possible to pick up and study the action potentials of muscles by means of modern oscillographs and discovered that the oscillogram varies with the power of the muscle to contract and thus provides a definite indication of good, fair, poor and vestigial muscular power as well as of normal and paralyzed muscles. By measuring the length of the curve per second and comparing it with the known millivolt deflection a definite figure for a muscle or a group of muscles may be obtained. Hansson says that "if this type of curve could be obtained by electrocardiograph with adequate amplification, the usefulness is obvious."

Experimental Poliomyelitis.—Toomey and Takacs¹²¹ in studying the portal of entry of poliomyelitis and how it passes into the central nervous system found in trying to repeat the work of Hurst and previous work by Toomey that 10 animals in which the virus had been injected into the sciatic nerve failed to acquire poliomyelitis. They then obtained a different strain of virus and found that animals which received injections of it in the sciatic nerve became ill with the disease. In view of the fact that both strains originally came from Flexner's M. V. strain, they conclude that there may be a quantitative difference in virulence between descendants of the same strain of poliomyelitis virus carried by different laboratories. A difference in quantitative virulence in strains of poliomyelitis virus would easily explain negative results following their injection into peripheral nerves. The results of the experiments support the theory of axonic spread of poliomyelitis virus.

Sabin and Ward¹²² inoculated the sciatic nerves of 8 monkeys, all of which became ill with poliomyelitis. Nasal secretions were collected on absorbent cotton plugs every twenty-four hours during the life of the monkeys. The nasal secretions collected during each twenty-four to forty-eight hours from several monkeys were pooled and tested for virus. The tests for the virus all gave negative results. The authors conclude that there was no evidence of centrifugal spread. Thus the finding of the virus in the human pharynx and in the intestines suggests these sites as portals of entry. Postmortem studies of the monkeys revealed no virus in olfactory bulbs, nasal mucosa, tonsils, salivary glands, adrenals, superior sympathetic ganglions, celiac ganglions or small intestine.

Wolf,¹²³ working with the Jungeblut-Sanders virus, carried out further studies on the possible transmission of the virus of human poliomyelitis to rodents as well

120. Hansson, K. G.: Electromyographic Studies in Poliomyelitis, *Arch. Phys. Therapy* **23**:261-266 (May) 1942.

121. Toomey, J. A., and Takacs, W. S.: Spread of Poliomyelitis Virus Along Axons of Peripheral Nerves, *Am. J. Dis. Child.* **63**:467-473 (March) 1942.

122. Sabin, A. B., and Ward, R.: Natural History of Experimental Poliomyelitis Infection: Studies on Centrifugal Spread and Elimination of Virus in Intrasciatically Inoculated Rhesus Monkeys, *J. Exper. Med.* **75**:107-117 (Jan.) 1942.

123. Wolf, A.: Studies in Rodent Poliomyelitis: Pathology of Murine and Cavian Poliomyelitis, *J. Exper. Med.* **76**:53-72 (July) 1942.

as to monkeys. Wolf studied the histologic changes of the S. K. rodent virus infection in white mice and guinea pigs submitted by Jungeblut and Sanders. He describes the lesions produced in mice and guinea pigs by inoculation of the virus and states that he has observed that in mice the virus apparently retains its affinity for the anterior horns of the spinal cord, but in a moderate degree. Associated with a marked increase in virulence of the virus, a strong affinity for the cerebral tissues, more particularly the olfactory centers, develops. When this murine variant of the virus is transmitted to the guinea pig, however, its original character is again revealed, and there is a reversion to a predominant affinity for the nerve cells of the anterior horns of the spinal cord.

Kramer, Geer and Himes¹²⁴ made studies on the continuous intravenous administration of hypotonic solution of sodium chloride in acute experimental poliomyelitis. They carried out seven experiments using 29 monkeys and conclude that the administration of hypotonic solution of sodium chloride to monkeys infected with poliomyelitis virus does not affect the course of the disease.

Tonsillectomy and Poliomyelitis.—Francis, Krill, Toomey and Mack¹²⁵ report a most interesting family incidence of poliomyelitis. The K family of Akron, Ohio, consisted of father, mother and 6 children. The children's ages ranged from 2½ years to 11 years. All the children were healthy on Aug. 1, 1942. On August 22, the 5 oldest children had tonsillectomies and the 4 oldest also had teeth extracted. On August 31 the 7 year old child became ill. By September 5, the 5 children who had been operated on all became ill with severe bulbar poliomyelitis, and 3 died. The father, the mother and the 1 child who had not been operated on showed no signs of illness. During the period the K family had poliomyelitis Akron was relatively free of the disease. The K children had had no contact with other patients with poliomyelitis, and no subsequent epidemic occurred in Akron. A search for possible contacts had remarkable results. The virus was recovered from the stools of 2 cousins living in a city 50 miles (80 kilometers) away with whom the K children had been in contact in June 1941. Four additional cousins in another family group, with whom the K children had lived for two weeks following June 1941, showed virus in their stools but did not get clinical poliomyelitis. No virus was obtained from 9 adult relatives or from cousins of two other family groups with whom contact was casual. Among 28 playmates a group of 3 children in one family was found to be carrying poliomyelitis virus. Toomey and Krill,¹²⁶ in another report made from the Children's Hospital in Akron and the division of contagious diseases of the City Hospital in Cleveland, show that 14, or 82 per cent, of 17 patients who had a tonsillectomy and adenoidectomy within thirty days prior to the onset of the illness became ill with bulbar paralysis. Among patients who had not had such operations 7, or 5 per cent, of 140 patients admitted to Children's Hospital and 23, or 19.4 per cent, of 118 patients admitted to City Hospital were stricken with bulbar paralysis. To explain the relationship between poliomyelitis and tonsillectomy Toomey and Krill consider two possibilities: (1) that poliomyelitis occurs as an accident during the course of mass immunization or exposure, during which time most or

124. Kramer, S. D.; Geer, H. A., and Himes, A. T.: Use of Continuous Intravenous Administration of Hypotonic Sodium Chloride (Retan Treatment) in Acute Experimental Poliomyelitis in Monkeys, *J. Immunol.* **44**:175-194 (July) 1942.

125. Francis, T., Jr.; Krill, C. E.; Toomey, J. A., and Mack, W. N.: Poliomyelitis Following Tonsillectomy in Five Members of a Family: Epidemiologic Study, *J. A. M. A.* **119**: 1392-1396 (Aug. 22) 1942.

126. Toomey, J. A., and Krill, C. E.: Tonsillectomy and Poliomyelitis, *Ohio State M. J.* **38**:653-655 (July) 1942.

all persons may harbor the virus and (2) that poliomyelitis has nearly an obligate affinity for gray fibers of either medullated or unmedullated nerves. Operation exposes the axis-cylinders of cut peripheral nerves and thus possibly makes absorption by gray fibers much easier. Or it may be that because of the operation new vascular networks are laid down, a process associated with deposition of new unmedullated fibers of the type which easily absorbs virus. They feel that in their locality it would be advisable to do tonsillectomies in the late spring.

Aycock¹²⁷ reviews the literature on tonsillectomy and its relation to bulbar poliomyelitis and presents rather conclusive statistics on 918 cases occurring in Massachusetts from 1927 through 1931 and on 743 cases occurring in Vermont from 1912 through 1931. He concludes that the absence of tonsils does not predispose to the paralysis of poliomyelitis but rather is a determinant as between the spinal and the bulbar type of the disease. From the Massachusetts report it was learned that of 210 patients with bulbar paralysis 122 or 58.1 per cent had had a tonsillectomy. Of the 638 patients with spinal paralysis 146, or 22.8 per cent, had had a tonsillectomy.

Seydell¹²⁸ made an exhaustive study of the literature and obtained statistics by addressing a form letter to each state board of health, to the United States Public Health Service and to thirty-five hospitals located in various parts of the country. It is difficult to evaluate his interpretations, since apparently his object in writing the paper was to prove that tonsillectomy does not affect the course of poliomyelitis. He hesitates to accept the full value of the statistics presented by Eley and Flake, with their high percentage of patients with bulbar poliomyelitis who had been tonsillectomized within thirty days, because these statistics take into consideration only those patients who were admitted to a single hospital and do not fully represent all who were included in the epidemic. A survey of the statistics accumulated in Seydell's paper shows that the total number of cases in which bulbar poliomyelitis followed a recent tonsillectomy was 48; the number of cases in which the spinal form of the disease occurred after this operation was 25. That is, there were almost twice as many cases of bulbar as of spinal poliomyelitis, and the author says, "The disparity is striking, and I can offer no explanation for it." [ED. NOTE.—Do the tonsillectomies explain the disparity?]

Early Treatment.—Cadham¹²⁹ reports on a method of collection of immune serum by which from June 1 to Sept. 15, 1941 80,000 cc. of blood was collected from 125 donors who had previously suffered from an attack of poliomyelitis. The donors returned at intervals, and from 65 to 120 cc. of blood was withdrawn from each donor each time. The serum was put up in vials containing 20 cc. for intramuscular injection during the preparalytic stage. Cadham stated that the clinical reports indicate that when the convalescent serum was used it was of therapeutic value.

Coggeshall and Maier¹³⁰ tested a number of sulfonamide compounds, sulfones and other compounds (principally heterocycles) for their effectiveness against two experimental virus infections in white mice. None of the drugs was effective in

127. Aycock, W. L.: Tonsillectomy and Poliomyelitis: Epidemiologic Considerations, *Medicine* **21**:65-94 (Feb.) 1942.

128. Seydell, E. M.: Relation of Tonsillectomy to Poliomyelitis, *Arch. Otolaryng.* **35**:91-106 (Jan.) 1942.

129. Cadham, F.: Convalescent Serum in Poliomyelitis, *Canad. Pub. Health J.* **33**:287 (June) 1942.

130. Coggeshall, L. T., and Maier, J.: Effect of Various Sulfonamides, Sulfones, and Other Compounds Against Experimental Influenza and Poliomyelitis Infections in White Mice, *J. Pharmacol. & Exper. Therap.* **76**:161-166 (Oct.) 1942.

delaying or preventing the development of the disease or in reducing the mortality from the infection. They feel that because of the considerable number of compounds tested and because many of them were representative of large groups of related chemicals, the reporting of their negative results is of value.

[ED. NOTE.—The results of this experimental investigation are in keeping with the clinical results that have been obtained in attempts at using sulfonamide compounds in treating virus diseases.]

The Council on Physical Therapy of the American Medical Association¹³¹ has published a pamphlet which graphically sets forth the details for the construction of a simple respirator which was prepared during an emergency in the Michigan epidemic of 1940. The respirator was constructed of two gasoline drums welded together and fitted with a hand-manipulated valve. This apparatus was attached by a hose to the one available respirator as a "trailer." Two children were placed in this "trailer," and women of the community worked the valve on the drums constantly for thirty-six hours until a mechanical automatic valve was made which allowed the homemade respirator to simulate the manufactured Drinker respirator. Details for the construction of the apparatus are available for distribution on application to the Council on Physical Therapy.

McLoughlin¹³² discusses the epidemic of poliomyelitis in 1941 in Georgia and points out that many patients have been kept alive by the early and continued use of the respirator. He describes the physics, physiology, technic and indications for use of the respirator and warns as to the contraindications for its use. He feels that the use of the respirator in properly selected cases will give excellent results and will prove of inestimable value. However, if it is used indiscriminately and routinely, without proper selection of patients, the results are bound to be disappointing, and statistically it will appear to be of little value in the saving of human life. On the other hand, a knowledge of the early signs of respiratory failure will permit the use of the respirator long before the weakened muscles have become exhausted. He warns that it must be remembered that bulbar types of paralysis do not as a rule show satisfactory improvement and that they account for the majority of disappointing results to be found after the use of the respirator.

The Kenny Treatment.—Much has been written on the Kenny treatment of poliomyelitis during the year 1942, and it was the chief topic of argument at the recent meeting of the American Academy of Orthopaedic Surgeons. Undoubtedly overenthusiastic lay publicity, personality clashes and a misunderstanding of terminology have prejudiced many physicians against Miss Kenny and her work. If one is interested in getting a fair appraisal of the studies which have been made on the Kenny treatment at the University of Minnesota, Krusen's¹³³ observations should be read. Dr. Krusen in his report traces the history of Miss Kenny's experiences in getting established in this country and gives many personal side-lights which are of interest. He points out that the Kenny concept of poliomyelitis does not conflict with the accepted idea that there is damage to the anterior horn cells in flaccid paralysis. Miss Kenny maintains, however, that something more than this occurs, that the major symptoms early in the disease are not so much due to flaccid paralysis as to three other symptoms: "muscular spasm," a con-

131. Simple Workable Respirator, report of the Council on Physical Therapy, J. A. M. A. **118**:535 (Feb. 14) 1942.

132. McLoughlin, C. J.: Respirators, and How to Use Them, Arch. Phys. Therapy **23**: 336-340 (June) 1942.

133. Krusen, F. H.: Observation on Kenny Treatment of Poliomyelitis, Proc. Staff Meet., Mayo Clin. **17**:449-460 (Aug. 12) 1942.

dition called "incoordination" and another condition given the descriptive name "mental alienation." "Muscular spasm" is defined as a group of symptoms including fibrillary twitchings (fasciculation), hyperirritability of the muscle to stretching and a more or less chronic state of contraction of the muscle fibers which frequently cannot be overcome even by great force. Krusen states that his own observations have convinced him that such spasm does exist during the early stages of poliomyelitis, that it may be widespread and that it is something more than the result of simple meningeal irritation, as was previously thought. A second major symptom, "incoordination," is described as being principally of two types: (1) that due to the spreading of motor impulses intended for a certain muscle to other muscles or groups of muscles because of such a condition as pain on attempted motion of the involved muscle or inability of that muscle to perform its proper function and (2) that occurring within the involved muscle itself, so that ineffective contraction is produced instead of a coordinated rhythmic contraction producing maximum motion at the insertion of the muscle. The third of the major symptoms mentioned is "mental alienation," which is described as the inability to produce a voluntary, purposeful movement in a muscle in spite of the fact that the nerve paths to that muscle are intact. This is a physiologic block which must be distinguished from the organic interruption resulting from the destruction of anterior horn cells by the disease. As an example of this unusual conception, which is difficult to accept, in a case of foot drop the gastrocnemius muscle is said to be in "spasm" and the dorsiflexor muscles are said to be "mentally alienated." According to this conception, the muscles which usually are spoken of as paralyzed in some instances are not truly so, although they may be, but are "mentally alienated" because of the spasm of the gastrocnemius muscle. It must be remembered that it is not claimed that "spasm," "incoordination" and "mental alienation" are the only mechanisms which are present in poliomyelitis. In an exceedingly severe infection enough anterior horn cells are destroyed at the outset to cause complete flaccid paralysis of certain muscles or parts, and spasm, if present at all, may be fleeting. Treatment for this condition is ineffective in preventing the paralysis. Space will not allow a complete review of Dr. Krusen's description of the treatment of "spasm," "incoordination" and "mental alienation." "Spasm" is treated by hot fomentations and by reeducation of the muscle after spasm is eliminated by focusing the patient's attention on the motion to be performed to establish "mental awareness." Reeducation of muscles depends on the relief of spasm, the teaching of mental awareness, the combating of incoordination and alienation and the retraining of neural pathways back to the nonfunctioning muscles. Dr. Krusen points out that the tremendous enthusiasm for the Kenny procedure seems to a large degree warranted, although it appears evident that some of the claims concerning it are too enthusiastic. He points out that some of the claims, such as "absolutely no deformities," are misleading, since some of the patients do have flail extremities after the Kenny treatment, and some of them walk with a Trendelenburg limp. These are certainly deformities. What the observers probably meant to say was that they had not seen such deformities as contractures and malalignment. Dr. Krusen feels that Miss Kenny's ideas are original, that she should be given full credit for having developed a new and extremely interesting concept of the symptoms of early poliomyelitis and the proper management of these symptoms, and that the Kenny method merits the close scrutiny of every physician.

[ED. NOTE.—Dr. Krusen's observations merit a close reading by every physician.]

Irwin¹³⁴ reports on the use of the Kenny therapy at Warm Springs, Ga., and states that the patients in the acute stage of the disease have been more comfortable and have had no limitation of motion in the joints and no contractures or scoliosis and that the period of convalescence has been materially shortened. However, all of these patients, although in good condition, have not been entirely cured of their paralysis. He is still convinced that some patients will always show a residual muscular weakness and that the degree of this weakness will be determined by the extent and distribution of the destruction in the anterior horn cells. Likewise, he feels that it will always be necessary to have permanent apparatus for some of these patients and that some type of surgical treatment designed for rehabilitation will always be done. But it is his hope that this method will offer a means whereby the number of braces that will have to be worn will be lessened and that the number of operations that must be performed will be reduced to a minimum. He states that his presentation can be considered neither an endorsement nor a critical analysis of the method, and he apparently intends to continue to use it with constant study over a sufficient period of time and when sufficient information has been obtained to disseminate it to the medical profession through the proper channels. In the meantime, he feels that it is important to protect the public against any abuse or misuse of this method of treatment.

Many articles have appeared in the literature during 1942 giving reports of the results of the use of the Kenny treatment. The majority of these reports have been in favor of the therapy. Daly and his associates¹³⁵ report the treatment of 71 patients. Twenty-eight, 2 of whom were nonparalytic, were treated by the Kenny method. Forty-three, of whom 10 were nonparalytic, were treated by the orthodox method. [ED. NOTE.—Just what the "orthodox" method is, is questionable.] Their conclusions are that the Kenny treatment is the treatment of choice. Pohl¹³⁶ reports on the cases of the first 26 patients treated in this country by Sister Kenny. The 26 cases are presented in tabular form, and the data given include the age, name and sex of the patient, the duration of symptoms, the muscles involved, the duration of hospitalization and the results of treatment. The conclusions are that the Kenny treatment should be immediately adopted as the fundamental treatment of poliomyelitis. Ober¹³⁷ emphasizes that the management of acute poliomyelitis should represent the combined efforts of the family physician, the orthopedist and a good nurse. He feels that the Kenny treatment is the correct treatment to use and points out that only a person skilled in the technic should use the Kenny treatment, since a great deal of damage can result from rough handling of patients and unskilled physical therapy. Stimson¹³⁸ in a report on the rationalization of the Kenny treatment points out that no treatment of poliomyelitis is satisfactory and that all treatment is directed along lines of symptomatic relief. He calls attention to the fact that there are four

134. Irwin, C. E.: Brief Résumé of Kenny Method of Treating Infantile Paralysis, South. Surgeon **11**:675-677 (Sept.) 1942.

135. Daly, M. M. I., and others: Early Treatment of Poliomyelitis with Evaluation of Sister Kenny Treatment, J. A. M. A. **118**:1433-1443 (April 25) 1942.

136. Pohl, J. F.: Kenny Treatment of Anterior Poliomyelitis (Infantile Paralysis): Report of First Cases Treated in America, J. A. M. A. **118**:1428-1433 (April 25) 1942.

137. Ober, F. R.: Pain and Tenderness During Acute Stage of Poliomyelitis, J. A. M. A. **120**:514-515 (Oct. 17) 1942.

138. Stimson, P. M.: Minimizing After Effects of Acute Poliomyelitis: Rationalization of Kenny Treatment, J. A. M. A. **119**:989-991 (July 25) 1942.

causes of muscular dysfunction in poliomyelitis: (1) primary loss of innervation, which is the only irremediable condition; (2) spasm of surviving muscles and muscle fibers; (3) muscular incoordination, and (4) mental alienation. He agrees that the Kenny treatment is the treatment of choice today, provided that it is given with the full knowledge that no treatment will help dead motor units and that the Kenny therapy will only rescue the muscles from the effects of spasm, muscular incoordination and mental alienation.

Steindler¹³⁹ and Steindler, Russin, Sheplan and Wolkin¹⁴⁰ in two most comprehensive and thorough papers reporting the studies at the Iowa Clinic on the use of the Kenny therapy and modifications thereof report the following conclusions: The entire pathologic concept of infantile paralysis must be changed from the old ideas of a purely motor deficiency originating in the anterior horn cells. The motor dysfunction seems to reach much higher and produces a state of confusion which blocks the use of the individual paralyzed muscles and leads to the adoption of complex substitutionary motions. These motions become habitual and are difficult to overcome unless special detailed instructions in training are given to patients along the lines outlined by Sister Kenny. Steindler and his associates do not believe that all fixation or all immobilization should be abandoned. They believe that when they are convinced of the soundness of the newer clinical observations in infantile paralysis, the application of common sense and of general biologic principles will make apparent the proper road of conduct, free from orthodoxy and from radicalism.

Knapp,¹⁴¹ in a further report on the studies at the University of Minnesota, based on more than two years of observation of the Kenny method of treatment of infantile paralysis, advances several theories as to the causes of muscular spasm, of mental alienation and of incoordination. In considering the possible mechanism for the production of spasm he presents several possible local causes, such as (1) inflammatory or toxic changes in the muscle itself and (2) circulatory changes resulting in localized anoxia, possibly caused by lesions of the sympathetic nervous system. He points out that it is well known that pain fibers in the muscles come entirely from blood vessels, so that local anoxia might explain the muscular tenderness as well as the spasm, and local anoxia if persistent might result in the development of contractures. Changes in the central nervous system may account for the spasm in the muscles: 1. There may be irritative lesions in the spinal cord. 2. Denervated muscle is hypersensitive to acetylcholine, which in infantile paralysis may be abundantly supplied through the uninvolved motor pathways, the sensory nerves and the autonomic endings. Here is an excellent mechanism whereby local spasm could be caused by pathologic change in the cord. 3. The spasm frequently changes rather rapidly in contractures which in time may become irreversible because of fibrous tissue replacement. Mental alienation is explained as probably being fundamentally a physiologic block in conduction, as contrasted with an anatomic block caused by destruction of anterior horn cells. The work of Bulbring and Burn, which showed that under conditions of perfusion impulses applied to the motor roots failed to be transmitted along the sciatic nerve to the gastrocnemius muscle of the dog when the vascular tone became low, and the well known

139. Steindler, A.: Contributory Clinical Observations on Infantile Paralysis and Their Therapeutic Implications, *J. Bone & Joint Surg.* **24**:912-921 (Oct.) 1942.

140. Steindler, A.; Russin, L. A.; Sheplan, L., and Wolkin, V.: Recent Changes in Concept of Treatment of Poliomyelitis, *Arch. Phys. Therapy* **23**:325-331 (June) 1942.

141. Knapp, M. E.: Kenny Treatment for Infantile Paralysis, *Arch. Phys. Therapy* **23**: 668-673 (Nov.) 1942.

condition of paralysis or apparent paralysis of the anterior tibial muscle which disappears after an operation to lengthen a contracted achilles tendon are cited as instances of probable mental alienation. Incoordination is explained as a disturbance in the normal motor patterns as a result of paralysis, alienation or spasm, in which new motor patterns are developed which must be restored to normal before normal action can occur.

[ED. NOTE.—Knapp presents many lines of thought for further investigation on this most interesting subject.]

Cole, Pohl and Knapp¹⁴² outline in minute detail the characteristic spasm and how it is detected in various areas of the body. They also give detailed instructions on the application of the Kenny treatment of spasm and muscle reeducation. Hansson¹⁴³ reviews the history of the treatment of poliomyelitis and points out that there are such diversions of opinion in regard to the therapy in poliomyelitis because it is difficult to estimate the relative value of any form of therapy. The basis of evaluation is the muscle-grading system, which varies with each examiner. He points out that Miss Kenny has no clinical data to show and that testimonials cannot be used to convince modern physicians. He feels that the most rational treatment of poliomyelitis is halfway between the early intensive treatment and the long immobilization. Lewin¹⁴⁴ endorses the Kenny therapy, as does Dyson.¹⁴⁵

Toomey¹⁴⁶ in his usual thorough manner describes the Toomey-Feiss method of treatment, whose salient features include elimination of immobilization, active and passive treatment and general physical therapy of the weak or paralyzed muscles, and manipulation and massage of the opposing stiffened muscles. He emphasizes the importance of early treatment by properly trained persons, under proper guidance. He describes the general treatment in minute detail. It has been adopted through trial and error methods during the past twenty years in treating over 1,400 patients in the acute stage of the disease. He feels that in his locality he could point to the work of one physician specializing in physical therapy whose results would compare favorably with those obtained in any clinic. Dr. Toomey points out that any treatment, early or late, followed by poor physical therapy will give poor results and warns that in being critical one should not lose a sense of proportion and "call a spade a steamshovel." He makes it plain that when one talks of the results of any one treatment only those patients with evidence of damage to the anterior horn cells, whether mild or severe, should be selected to demonstrate its benefit. Toomey discusses the various concepts of the Kenny therapy and states that any disagreement he might have with Miss Kenny is not with her method of treatment. After a week spent at the University of Minnesota observing the patients treated by the Kenny method, he points out that Miss Kenny has an uncanny knowledge of bodily mechanics and the uses to which muscles can be put. He believes that most of her results are due to a superior knowledge of muscle reeducation, in which she is a past master. Toomey does not agree with

142. Cole, W. H.; Pohl, J. F., and Knapp, M. E.: Kenny Method of Treatment for Infantile Paralysis, *Arch. Phys. Therapy* **23**:399-418 (July) 1942.

143. Hansson, K. G.: Present Status of Physical Therapy in Anterior Poliomyelitis, *Physiotherapy Rev.* **22**:3-5 (Jan.-Feb.) 1942.

144. Lewin, P.: Kenny Treatment of Infantile Paralysis During Acute Stage, *Illinois M. J.* **81**:281-296 (April) 1942.

145. Dyson, J. E.: Kenny Treatment of Infantile Paralysis of Acute Stage, *J. Iowa M. Soc.* **32**:297-298 (July) 1942.

146. Toomey, J. A.: Early Treatment of Poliomyelitis, *J. Pediat.* **21**:353-373 (Sept.) 1942; Treatment of Infantile Paralysis in Acute Stage, *Arch. Phys. Therapy* **23**:650-662 (Nov.) 1942.

Miss Kenny's theories but admits that she gets good results with her methods and feels that her classification of muscles is logical and that her meticulous program of reeducation leaves little to be desired in the after-care of infantile paralysis.

McCarroll¹⁴⁷ calls attention to the many glowing reports on the results of treatment of acute anterior poliomyelitis by numerous and widely different forms of physical therapy during the past quarter century. He compares the results of the various forms of treatment in 245 recent cases of poliomyelitis (487 involved extremities) observed at the St. Louis unit of the Shriners' Hospital for Crippled Children between 1935 and 1941. From the findings he concludes that it is safe to assume that the results in anterior poliomyelitis can be more adequately explained on the basis of the underlying pathologic process than according to the form of the early treatment used. His study included no patients treated by the Kenny method, but he states that it has been his privilege to visit briefly the various hospitals in Minneapolis and see some of the patients treated under Miss Kenny's supervision. He believes that for symptomatic treatment in the acute stage this method may offer definite advantage but that it falls far short of supplying the answer to the problem. McCarroll feels certain that the Kenny method in time will take its place among the others offered to the field of physical therapy as having been tried but found wanting. He feels that physical therapy will never prove to be the answer, that the control of poliomyelitis will undoubtedly some day be brought about through prevention and not through cure and that the sooner more of the available funds are used for research work in the field of immunology, the sooner the investment will begin to yield satisfactory returns.

Operations.—The Research Committee of the American Orthopaedic Association¹⁴⁸ in a most excellent report of a survey of end results on stabilization of the paralytic shoulder summarizes the results for 148 patients, of whom 101 had shoulder fusions. The average position of fusion in this series was 40 degrees abduction, 10 degrees flexion and 40 degrees internal rotation. The average active rotation of the scapula was 70 degrees. The committee believes that the best position for fusion, if there is fair to good power in both the trapezius and the serratus anterior muscle, is 45 to 55 degrees of abduction, 15 to 25 degrees of flexion and 15 to 25 degrees of internal rotation. In analyzing the position for fusion they point out that a greater range of motion of the scapula develops in children than in adults. The proper function of fused shoulders depends on good power in the upper part of the trapezius muscle and the upper two thirds of the serratus anterior muscle. The trapezius starts abduction, and the serratus anterior finishes it. When the serratus is powerless the trapezius can abduct only 45 degrees. The range of motion is better in patients operated on when under 12 years of age, and the operation can be done any time after the patient is 6 years of age. A majority of the shoulders were fused by the operation described by Gill, and the average time of immobilization in plaster was three and one-half months. The committee concludes that arthrodesis of the shoulder is the operation of choice in all cases of poliomyelitis in which there is complete paralysis of the deltoid muscle.

147. McCarroll, H. R.: Role of Physical Therapy in Early Treatment of Poliomyelitis, *J. A. M. A.* **120**:517-519 (Oct. 17) 1942.

148. Survey of End Results on Stabilization of Paralytic Shoulder, report of Research Committee of American Orthopaedic Association, *J. Bone & Joint Surg.* **24**:699-707 (July) 1942.

Williamson, Moe and Basom¹⁴⁹ report the results of the use of fascial transplants for paralysis of the abdominal muscles as described by Lowman. Their study includes 31 operative procedures on 29 patients, all of whom had some degree of paralysis of the abdominal wall as a result of poliomyelitis. Seven of the patients had been operated on from six to ten months before the report was written, 7 one year, 4 two years, 4 three years, 3 five years, and 4 six years. The authors conclude that the operation is worth while from the standpoint of stabilizing the abdominal wall, that the patient's fatigue is lessened, that control of the function of the bladder and the bowels is improved, that sitting and walking can be performed better and that the gait is improved. However, the operation did not prove to be of value in the prevention of scoliosis.

Irwin,¹⁵⁰ in describing a controlled method of operative correction for genu recurvatum resulting from poliomyelitis, discusses the types and causes of genu recurvatum following poliomyelitis and describes a technic of osteotomizing the upper end of the tibia and fibula, with control of the fragments by the use of a Kirschner wire in the proximal fragment to hold it in hyperextension while the lower fragment is carried posteriorly for realignment. The operation is done through two incisions, and the knee joint is not disturbed.

[ED. NOTE.—This operation appears to be a simple procedure with sound mechanics which gives one perfect control over the fragments.]

VI. NEUROMUSCULAR DISORDERS EXCLUSIVE OF INFANTILE PARALYSIS

PREPARED BY WINTHROP M. PHELPS, M.D., BALTIMORE

During 1942 there was a definite decrease in the volume of literature dealing with neuromuscular disorders. This was to be expected, because of the great necessity for interest in the problems of military medicine and the diversion of research into the specific problems of war. The work in the field of war injuries with neuro-orthopedic complications has not progressed far enough for any end results in this field to be published. For example, there were no articles on neurologic injuries to the spine, although such injuries are certainly being seen as the war progresses. The more acute phases of such conditions are probably being discussed in connection with war injuries in general.

The references in this field can be classified under five headings: (1) injuries to the peripheral nerves, (2) cerebral palsy, (3) paralysis of the brachial plexus, (4) tabetic arthropathies and (5) muscular dystrophy.

Injuries to the Peripheral Nerves.—McMurray¹⁵¹ points out the uses and abuses of splints and corrective apparatus in the treatment of injuries of the nerves. The incorrect application of a splint or the use of a splint without regard to the type of neural involvement is too often carried out. Hight¹⁵² also describes the proper splinting for injuries of peripheral nerves.

Hudson¹⁵³ describes a method of transplanation of the external peroneal nerve after injury. This nerve is easily injured because of its superficial course

149. Williamson, G. A.; Moe, J. H., and Basom, W. C.: Results of Lowman Operation for Paralysis of Abdominal Muscles, *Minnesota Med.* 25:117-120 (Feb.) 1942.

150. Irwin, C. E.: Genu Recurvatum Following Poliomyelitis: Controlled Method of Operative Correction, *J. A. M. A.* 120:277-280 (Sept. 26) 1942.

151. McMurray, T. P.: Uses and Abuses of Splints and Other Instruments in Treatment of Nerve Lesions, *Brit. J. Phys. Med.* 5:20-42 (Feb.) 1942.

152. Hight, W. B.: Splintage of Peripheral Nerve Injuries, *Lancet* 1:555-558 (May 9) 1942.

153. Hudson, O. C.: Lesions of External Peroneal Nerve: Relief by Transplantation, *J. Internat. Coll. Surgeons* 5:223-224 (May-June) 1942.

around the head of the fibula. He resects the upper portion of the fibula, allowing the nerve to take a shorter route, especially when correction of genu valgum is indicated surgically. This procedure is especially indicated for persistent pain over the distribution of the external peroneal nerve. He reports 4 cases in which relief of pain was secured.

Maurer¹⁵⁴ describes the complications and sequels of fractures with concomitant injuries to the peripheral nerves in general, and Marques Tourinho¹⁵⁵ reports cases of specific lesions of the radial nerve complicating fractures of the humerus. Kernwein and Lyon¹⁵⁶ describe an interesting complication of complete severance of the sciatic nerve in which a neuropathic arthropathy of the ankle developed.

Cerebral Palsy.—Green and McDermott¹⁵⁷ have made an extensive study of 421 orthopedic operations on 160 patients with spastic paralysis carried out over the past fifteen years. They carefully limited the number of patients operated on, because:

- (a) Surgical procedures are an adjunct in the general plan of treatment of cerebral palsy.
- (b) Orthopedic operations on patients with extrapyramidal cerebral palsy [athetosis for example] are not often helpful.
- (c) Operations are indicated in only a certain proportion of cases of spastic paralysis depending on the nature of the deformity and the general status of the patient.

Within these wise limitations, they found that arthrodesis for deformities of the feet produced the greatest number of good results. There were many good results from the lengthening of the heel cord and transplantation of muscles, provided certain principles were observed.

Lengthening of the hamstring tendons was more successful when it was accompanied with lengthening of the upper end of the gastrocnemius muscle. The results of obturator neurectomy with adductor myotomy were disappointing. Division of the branch of the median nerve to the pronator teres was helpful in correcting pronation, and transplantation of the flexor carpi ulnaris to the flexor carpi radialis corrected both the flexion and the pronation deformity of the wrist. They state that many poor results were due to inadequate postoperative care and training.

Denhoff and Bradley¹⁵⁸ discuss the use of curare in the therapy of cerebral palsy. The treatment of cerebral palsy consists essentially of muscle training combined with physical reeducational procedures. The use of curare produced improved relaxation and reduction of spasticity lasting about four days, which accelerated the response to the muscle training and reeducational program.

Carlson¹⁵⁹ describes cerebral palsy in general and details the treatment of the spastic, ataxic and athetoid types. He emphasizes the necessity for visual training and suggests the use of the microphone and loud speaker in speech training. He also emphasizes the great necessity for thorough academic education.

154. Maurer, J. F.: Injuries to Peripheral Nerves, *J. Indiana M. A.* **35**:620-622 (Nov.) 1942.

155. Marques Tourinho, M.: Fractures of the Humerus and Lesions of the Radial Nerve, with Report of Cases, *Rev. brasil. de ortop. e traumatol.* **3**:144-153 (Jan.-Feb.) 1942.

156. Kernwein, G., and Lyon, W. F.: Neuropathic Arthropathy of Ankle Joint Resulting from Complete Severance of Sciatic Nerve, *Ann. Surg.* **115**:267-279 (Feb.) 1942.

157. Green, W. T., and McDermott, R. J.: Operative Treatment of Cerebral Palsy of Spastic Type, *J. A. M. A.* **118**:434-440 (Feb. 7) 1942.

158. Denhoff, E., and Bradley, C.: Curare Treatment of Spastic Children: Preliminary Report, *New England J. Med.* **226**:411-416 (March 12) 1942.

159. Carlson, E. R.: Treatment of Infantile Cerebral Palsy, *Northwest Med.* **41**:160-163 (May) 1942.

Ross, Norfleet and Löwenbach,¹⁶⁰ who have studied the electroencephalogram in cases of cerebral palsy, show that it may give information regarding the localization and extent of cerebral lesions but that it is not of additional clinical diagnostic value and gives no additional information whatever regarding intelligence. It probably has value for determining susceptibility to convulsive seizures.

Johow¹⁶¹ and Baker¹⁶² have contributed independently to the therapy of cerebral palsy and Phelps¹⁶³ points out the increased improvement in cerebral palsy when there is a close relation between physical therapy and occupational therapy in the general treatment. Each type of therapy supplements the other, while neither is sufficient for the entire program.

Paralysis of the Brachial Plexus.—Caritat¹⁶⁴ describes the surgical and other general orthopedic procedures in the care of obstetric paralysis. Patterson¹⁶⁵ also discusses this subject.

Tabetic Arthropathies.—Despontin and Corsellas¹⁶⁶ describe fractures of the calcaneum and present a case of tabetic arthropathy of the knee with spontaneous fracture of the calcaneum.

Muscular Dystrophy.—Keith¹⁶⁷ presents a careful study of the effects of administration of vitamin B₆ (pyridoxine hydrochloride) on patients with pseudo-hypertrophic muscular dystrophy. Although doses of from 50 to 500 mg., administered hypodermically, were used, none of the patients showed any improvement in muscular strength. In some, according to the case reports, there was no advancement of the dystrophy during the period of observation, but in most there appeared to be no change whatever in the progress of the disease.

Pohl and Baethke¹⁶⁸ have presented the results of vitamin E therapy (oral) in 15 cases of progressive dystrophy without appreciable results in the control of the condition. For other reports in this field, reference is made to the paper of Cordero.¹⁶⁹

Hawke¹⁷⁰ investigated also the effects of vitamins B and E in the dystrophies. In 7 cases vitamin B₁ (thiamine hydrochloride), a placebo, pyridoxine hydrochloride, alpha tocopherol (series A) and alpha tocopherol (series B) were tried in succession. Negligible results were obtained with all the materials used, and some subjective improvement was noticed with the placebo as well as with the vitamins.

160. Ross, I. S.; Norfleet, G. M., and Löwenbach, H.: Cerebral Palsy and Electroencephalogram, *South. Med. & Surg.* **104**:613-616 (Nov.) 1942.

161. Johow, A.: Therapy of Little's Disease, *Rev. chilena de pediat.* **13**:337-342 (April) 1942.

162. Baker, F.: Physical Therapy in Cerebral Palsy, *Arch. Phys. Therapy* **23**:473-481 (Aug.) 1942.

163. Phelps, W. M.: Correlation of Physiotherapy and Occupational Therapy in Treatment of Cerebral Palsy, *Occup. Therapy* **21**:152-156 (June) 1942.

164. Caritat, R. J.: Surgery and Orthopedics in Nervous Disorders of Childhood, *Rev. chilena de pediat.* **13**:352-361 (April) 1942.

165. Patterson, R. L., Jr.: Obstetrical Paralysis, *Arch. Phys. Therapy* **23**:83-88 (Feb.) 1942.

166. Despontin, A. E., and Corsellas, M. F.: Tabetic Arthropathy of the Knee with Spontaneous Fracture of Calcaneum: Case, *Rev. méd. latino-am.* **27**:606-612 (March) 1942.

167. Keith, H. M.: Vitamin B₆ (Pyridoxine Hydrochloride) in Treatment of Pseudo-hypertrophic Muscular Dystrophy Among Children, *J. Pediat.* **20**:200-207 (Feb.) 1942.

168. Pohl, J. F., and Baethke, D.: Vitamin E in Progressive Muscular Dystrophy: Failure of Oral Administration in Fifteen Cases, *Am. J. Dis. Child.* **64**:455-461 (Sept.) 1942.

169. Cordero, J.: Pseudohypertrophic Progressive Muscular Dystrophy, *Eol. Asoc. méd. de Puerto Rico* **34**:211-217 (June) 1942.

170. Hawke, W. A.: Vitamin Therapy of Muscular Dystrophy, *Canad. M. A. J.* **47**:153-155 (Aug) 1942.

The author concludes: "In no cases did any definite improvement occur."

[ED. NOTE.—In the last three years much attention has been given to the use of vitamin B₆ (pyridoxine hydrochloride) and vitamin E (alpha tocopherol), mainly because of the similarity of vitamin B and E deficiencies in rats and other experimental animals to the dystrophies and myasthenias in man. However, the great preponderance of evidence, which seems to be increasing, is to the effect that little, if any, demonstrable improvement has resulted from the use of either vitamin B₆ or vitamin E alone or from the combination of the two. The importance of these vitamins should be kept in mind, however, since occasionally conditions actually due to deficiency may be encountered which rather closely resemble the dystrophies and for these, of course, administration of the vitamins would prove effective.]

VII. TUMORS OF BONE AND OF SYNOVIAL MEMBRANE

PREPARED BY HENRY W. MEYERDING, M.D., ROCHESTER, MINN.

Tumors of Synovial Membrane.—Gross and Cameron¹⁷¹ report a case of "synovialoma." Including theirs, the literature contains reports of 49 cases in which a tumor has been derived from the synovial membrane. In 1936 Knox collected 22 cases of this type of tumor and added 3 of her own. Berger, in 1938, collected 24 cases and reported 5 of his own. A year later, in 1939, Coley and Pierson reported 15 cases, and since that time 4 more cases have been added. Synovial tumors have been termed "synovioma," "synovialoma," "synovial sarcoma," and "synovial sarco-endothelioma." In the majority of cases the tumor is malignant. Metastasis may occur five to ten years after excision of the tumor. In the case reported by Gross and Cameron, the patient was a white American woman 57 years of age. The synovialoma had arisen from the suprapatellar pouch. It apparently had been growing for thirty years, and its cellular features indicated that it was benign. The patient was alive five years after excision of the tumor.

Briggs¹⁷² discusses 9 cases of synovioma records of which are on file at the Army Medical Museum. This series includes tumors arising from the articular capsule, the bursal wall and the tendon sheath. Lawrence Smith was the first to group such tumors together because they had a synovial lining. The growth may arise from the outer layer of the synovial membrane, which is composed of dense fibrous connective tissue. If so, it may be hard to distinguish it from fibrosarcoma. It also may arise from the inner layer, which is more cellular and is thought to secrete synovia. In the latter instance the tumor is prone to produce villi. The 9 tumors reported on occurred when the patients were 17 to 42 years of age. Four of the patients were males and 5 females. A history of mild trauma was present in 3 cases. The majority of the tumors were situated in the lower extremity; 5 were situated about the knee, 2 about the ankle, 1 in the foot and 1 in the forearm. The importance of detailed gross and microscopic examination of the tumor at the time of operation is stressed. In none of the cases was the diagnosis made preoperatively. There was nothing characteristic about the history or the clinical appearance of the synovial membrane. Briggs believes that complete excision of the tumor is the method of choice when it appears encapsulated and it can be removed together with a margin of healthy tissue. If complete excision cannot be carried out without injury to important structures, amputation should be per-

171. Gross, P., and Cameron, D. W.: Synovialoma, *Arch. Path.* **33**:687-690 (May) 1942.

172. Briggs, C. D.: Malignant Tumors of Synovial Origin, *Ann Surg.* **115**:413-426 (March) 1942.

formed. He further states that it is difficult to evaluate the result of radiation therapy for this type of lesion but that it seems a reasonable adjunct to excision.

Sutter and Levy Boladeres¹⁷³ state that some synoviomas which recur after operation can be considered benign. The subsequent clinical course and histologic appearance are similar to those of other benign tumors, namely xanthoma, fibroma and chondroma. These do not invade neighboring tissues. He reports a case in which the tumor behaved like a malignant tumor. He says that this type of synovioma does occur, although it is observed less frequently than the benign type. He says that in the course of operation the surgeon should observe whether the tumor arises from the synovial membrane. Any tumor which involves a joint, tendon or serosal membrane should be carefully studied microscopically after confirmation of malignancy. The tumor should be treated surgically because radiotherapy has proved to be inadequate for tumors of this type.

Haggart¹⁷⁴ reports a case of synovioma of the knee joint in which a diagnosis of cystic swelling of the lateral region of the left knee had been made before operation. The tumor was exposed by an elliptic incision, which left intact the skin directly over it. The adherent cystic mass was separated from the deep fascia, the capsule of the knee joint, the periosteum over the head of the fibula and the common peroneal nerve. A tail-like projection entered the knee joint posterior to the collateral ligament; a portion of the capsule, the external semilunar cartilage and the portion of the synovial membrane from which the tumor had originated were excised. In order to close the defect created by the excision, a "releasing" incision was made and Thiersch skin grafts were applied to the secondary wounds. The patient was walking with crutches on the twelfth day after operation, returned to work during the sixth week and has remained well for more than eight years.

A case of chondromatous metaplasia of the synovial membrane of the knee is reported as 1 of the Cabot cases.¹⁷⁵ The patient sought medical advice because of pain and swelling of the knee of nine months' duration. There had been no limitation of motion until two weeks before the patient was seen, when the knee had become stiff. There were no systemic reactions except malaise. The knee was swollen and hot; there was tenderness in both tibiofemoral fossae; the lymph nodes in both groins were swollen but not tender. Laboratory tests did not reveal any abnormality. Roentgenographic examination disclosed finely granular calcification along the lateral margin of the left knee joint. Aspiration obtained slightly cloudy, orange-colored synovial fluid. The fluid contained a normal amount of mucin and numerous erythrocytes and leukocytes. At operation the knee joint was found to be packed with split pea-sized pearly masses, some of which were attached to the synovial membrane. These were removed and synovectomy was performed. Microscopic examination showed that the masses were composed almost entirely of cartilage, and cartilaginous foci were present within the synovial membrane. When the foci developed in the villi they sometimes became pedunculated and sometimes broke off and formed joint "mice."

O'Donoghue¹⁷⁶ reports a case of xanthoma of the knee in which a preoperative diagnosis of fracture of the medial meniscus was made. The tumor was solitary,

173. Sutter, R., and Levy Boladeres, J.: Synovioma of Wrist, *Bol. Liga contra el cáncer* **17**:193-200 (July) 1942.

174. Haggart, G. E.: Synovioma of Knee Joint: Case Report, *J. Bone & Joint Surg.* **24**:438-442 (April) 1942.

175. Chondromatous Metaplasia of the Synovia of the Knee Joint, Cabot Case 28122, *New England J. Med.* **226**:500-501 (March 19) 1942.

176. O'Donoghue, D. H.: Case of Xanthoma of Knee Joint, *J. Bone & Joint Surg.* **24**: 940-941 (Oct.) 1942.

pedunculated and well delineated. He points out the extreme similarity of the symptoms of discrete tumors to those of rupture of the medial meniscus.

Charache¹⁷⁷ reports 65 cases of tumor of the tendon sheaths. The tumors were classified as ganglion in 60 cases, as lipoma in 2 cases and as hemangioma, fibroma and spindle cell sarcoma in 1 case each.

Localized Cysts of Bone.—Aldredge¹⁷⁸ evaluates the results of various forms of therapy in 152 cases of localized fibrocystic disease of bone. His survey denotes that only two methods of treatment are indicated in cases in which the lesion is operable: (1) resection and (2) bone grafting after curettage of the cystic cavity. Irradiation should be reserved for cases in which the lesion is inoperable. He reports 2 cases in which neoplastic changes occurred many years after the use of radiation therapy. Disturbances and arrest of epiphysial growth commonly occurred after treatment by irradiation.

Jaffe and Lichtenstein¹⁷⁹ describe solitary unicameral cyst of bone as an independent and distinct lesion and do not regard it as a phase of fibrocystic disease of bone. It is uncommon, occurs during childhood or adolescence and affects long tubular bones, especially the upper part of the humerus. It contains fluid, causes a thinning and expansion of the cortex and is lined by thin connective tissue. These authors report 19 cases. Fourteen of the patients were males. In 9 of the cases the lesions were situated in the upper part of the humerus and in 4 the upper part of the femur was involved. Clinically, patients have little or no pain, and the cyst attains a large size before it is discovered or before pathologic fracture occurs. It is most commonly situated in the upper end of the diaphysis near the epiphysial line; it rarely, if ever, goes beyond it. As the acute stage subsides, the cyst appears to become displaced farther away from the epiphysial plate and may move several inches in the course of a few years. It is in the latent and static stage that healing occurs most promptly following operation. Such a lesion cannot be readily distinguished roentgenologically from fibroma, enchondroma or localized fibrous dysplasia. In discussing the pathogenesis the authors subscribe to the theory of Pommer that solitary cyst of bone results from encapsulation and alteration of a focus of intramedullary hemorrhage.

Bick¹⁸⁰ says that some solitary cysts may be early manifestations of a generalized disease. He stresses the value of the clinical history and findings. He has not been favorably impressed by aspiration biopsy and says that examination of frozen sections is reliable for determining the malignancy or benignancy of the lesion.

[ED. NOTE.—Aspiration biopsy frequently fails to supply satisfactory tumor tissue. Incision and removal of a section of typical tumor tissue is much more dependable, and examination of frozen sections has been found fairly satisfactory.]

Ferrari¹⁸¹ reports a case of simple cyst of the tibia in which the patient was 17 years of age. With the patient under spinal anesthesia, the cavity was evacuated and the wall adjacent to the cyst was removed. The wound was closed without

177. Charache, H.: Tumors of Tendon Sheaths, *Arch. Surg.* **44**:1038-1052 (June) 1942.

178. Aldredge, R. H.: Localized Fibrocystic Disease of Bone: Results of Treatment in One Hundred and Fifty-Two Cases, *J. Bone & Joint Surg.* **24**:795-804 (Oct.) 1942.

179. Jaffe, H. L., and Lichtenstein, L.: Solitary Unicameral Bone Cyst, with Emphasis on the Roentgen Picture, the Pathologic Appearance and the Pathogenesis, *Arch. Surg.* **44**:1004-1025 (June) 1942.

180. Bick, E. M.: Differential Diagnosis of Solitary Cystic Areas in Bone, *J. Mt. Sinai Hosp.* **8**:1225-1231 (March-April) 1942.

181. Ferrari, R. C.: Simple Cyst of Tibia: Case with Recovery After Surgical Therapy, *Bol. d. Inst. clín. quir.* **18**:396-401 (June) 1942.

drainage; the patient was observed for four years. At the end of this time it was found that the cavity had been replaced by bone and the defect could not be noted. He states that Ivanissevich reported a case of simple cyst of the femur complicated by fracture. He emphasizes that fracture through a cyst will frequently result in cure because the callus obliterates the cavity and says that a cyst may occur after fracture. Furthermore, he mentions a case of cyst of the tibia that was reported by Nicolini. The patient was 22 years of age. Radiotherapy had been tried without beneficial result. After curettement and evacuation of the cavity and packing with iodoform gauze, the lesion completely healed.

Ortiz Tirado¹⁸² says that formerly surgeons thought that any loose bone should be removed in order to prevent formation of sequestrums. In inexperienced hands, there was abuse of this principle in cases of comminuted fracture. He states that even in recent years he has seen removal of fragments which caused a severe problem in determining the type of treatment for the loss of bone substance. He advocates the use of catgut, kangaroo tendon and wire to hold the fragments firmly in place. He says that he has had no trouble in obtaining union. He does not use plates for fixation, because they are a source of postoperative periosteal pain. He advocates the use of bone chips to fill cavities that have been formed by curettement of bone. He reports 1 case of generalized osteitis fibrosa cystica of the femur in which he curetted the cystic cavity and filled it with bone chips. The patient did not have any pain. Ortiz Tirado says that fragments of bone should not be used if infection is present. In a clean wound, however, every small fragment will help form good callus.

Hand-Schüller-Christian Disease (Eosinophilic or Solitary Granuloma).—Green and Farber¹⁸³ have collected 10 cases of this condition. In all of these cases the patients were children less than 12 years of age. In 6 cases the lesions were multiple, and in 4 they were single. The authors describe the condition as a benign destructive lesion of bone and state that the roentgenographic contour of the lesions was variable and usually consisted of a "punched-out" effect. The cortex was not expanded, and there was minimal reaction of bone about the lesion. The flat and irregular bones and the bones of the extremities closest to the trunk were almost always involved. The distribution and appearance of multiple lesions resembled those of metastatic malignant lesions and of multiple myeloma. Single lesions simulated a cyst of bone, osteomyelitis or a malignant lesion. Symptoms were attributable wholly to the local lesion; that is, they consisted of pain and swelling. There was no particular systemic reaction. Laboratory findings were all within normal limits except for the presence of eosinophilia of a mild degree. The microscopic picture usually is as follows: In cases in which the lesions were observed in an early stage of development, destruction of bone and cellular infiltration were observed. The cells of the infiltrate were predominantly mature eosinophils or eosinophilic myelocytes and large mononuclear cells. A variable number of plasma cells, lymphocytes and polymorphonuclear leukocytes were present. The scarlet red stain revealed stainable lipid, but tests for sphyngomyelin were negative. In cases in which the lesions were advanced, eosinophils were not present in the infiltrate. There was a fibroblastic reaction. Large vacuolated mononuclear cells predominated and later might be identical with the "foam" cells of a typical xanthoma. Treatment in this series of cases consisted of roentgen therapy, partial excision and curettage. Most lesions responded to small doses of roentgen rays.

182. Ortiz Tirado, A.: Bone Tissue as Filling Material in Loss of Substances, *Cir. y cirujanos* 10:65-70 (Feb. 28) 1942.

183. Green, W. T., and Farber, S.: "Eosinophilic or Solitary Granuloma" of Bone, *J. Bone & Joint Surg.* 24:499-526 (July) 1942.

Spontaneous healing occurred in 2 cases. Nine patients seemed entirely well after an average follow-up of more than six years, and 1 died of unknown cause. The authors state that the disease is "not a distinct new entity, but a variant of the basic process of which the clinical pictures known as Hand-Schüller-Christian's disease and Letterer-Siwe's disease are other examples."

In an article entitled "Eosinophilic Granuloma and Certain Other Reticulo-Endothelial Hyperplasias of Bone," Gross and Jacox¹⁸⁴ present the following conclusions:

1. Eosinophilic granuloma of bone is not a new nor distinct entity. It is a reticulo-endotheliosis and is probably identical with those cases of Hand-Christian's disease which have been reported to have had solitary lesions. It is also closely related to certain other reticuloendothelial hyperplasias.

2. The interrelationship demonstrated between eosinophilic granuloma and solitary xanthoma of bone, Hand-Christian's and Letterer-Siwe's disease and the existence of cases with features intermediate between these so-called entities make a sharp distinction between them of doubtful validity.

3. Since there are no pathologic, roentgenographic or other decisive features known at present which are distinctive for any one of those reticuloendothelioses, the need for further study, including routine biopsy, in this type of cases is apparent.

Thurm¹⁸⁵ reports a case of eosinophilic granuloma of bone in which multiple osseous lesions were present. The only other case of multiple eosinophilic granulomas of bone was reported by Farber, but he chose to designate the disease as a form of Hand-Schüller-Christian disease. In the case reported by Thurm, lesions were found in both femurs and in four ribs. A low grade fever, moderate leukocytosis and a moderately increased sedimentation rate were the only other essential findings. The lesions showed a tendency to heal spontaneously as well as after curettage. The roentgenographic appearance of the lesions rules out some types of chronic osteomyelitis, metastasis of a malignant tumor and Ewing's tumor.

Benign Osteogenic Tumors.—Osteoma: Horwitz¹⁸⁶ presents a case of osteoid-osteoma (Jaffe-Lichtenstein) of the right astragalus. The patient was a boy 16 years of age. Horwitz mentions that this lesion may be clinically and roentgenographically interpreted as osteomyelitis or as abscess of bone. It usually is unassociated with fever or with increased local heat. Clinical laboratory findings usually are normal. The roentgenogram usually demonstrates a radiolucent area in the bone. Proliferation of bone depends on the site of the lesion. Osteosclerosis may dominate the picture and lead to a mistaken diagnosis of sclerosing nonsuppurative osteomyelitis of Garré or intracortical abscess of bone. Jaffé interpreted the pathologic features as those of benign osteogenic tumor of bone. There usually is a proliferating, vascular osteoblastic tissue with occasional osteoclasts; later there is osteoid tissue which undergoes calcification.

Barron¹⁸⁷ reports a case of osteoid osteoma of the right os calcis. After excision complete cure apparently was obtained. He states that the history of persistent pain that was relieved by acetylsalicylic acid, the roentgenologic appearance and the dramatic relief of pain following excision are all typical of the condition. Furthermore, he states that owing to roentgenologic findings, the condition has been mis-

184. Gross, P., and Jacox, H. W.: Eosinophilic Granuloma and Certain Other Reticulo-Endothelial Hyperplasias of Bone: A Comparison of Clinical, Radiologic and Pathologic Features, *Am. J. M. Sc.* **203**:673-687 (May) 1942.

185. Thurm, A. S.: Eosinophilic Granuloma of Bone: Report of Case with Multiple Bone Lesions, *Bull. Hosp. Joint Dis.* **3**:9-16 (Jan.) 1942.

186. Horwitz, T.: Osteoid-Osteoma of the Astragalus, *Radiology* **39**:226-228 (Aug.) 1942.

187. Barron, L. J.: Osteoid-Osteoma of the Right Os Calcis: Case Report, *Bull. Hosp. Joint Dis.* **3**:141-145 (Oct.) 1942.

labeled "chronic osteomyelitis with a bone abscess or with an annular sequestrum," "sclerosing nonsuppurative osteomyelitis of Garré" or "intracortical disease of bone."

[ED. NOTE.—Further study of this group of tumors will have to be made and a larger series of cases will have to be observed over a period of years before there is a thorough understanding of the lesion.]

Chondroma: Jaffe and Lichtenstein¹⁸⁸ give the name "benign chondroblastoma of bone" to a rare lesion previously called "calcifying" or "chondromatous variant of giant cell tumor" or "chondrosarcoma" or "osteogenic sarcoma." The tumor starts in an epiphysis of some long bone and may extend to the articular surface of the epiphysis and even into the metaphysis; however, it rarely obtains a diameter of more than 3 to 5 cm. Other authors have found that this lesion has a predilection for the upper part of the humerus, but Jaffe and Lichtenstein did not find this to be so. Males predominate, and the patients are almost always in adolescence or past adolescence when seen. The roentgenographic appearance is helpful in making a clinical diagnosis. They describe the pathologic changes in detail and say that the most distinctive feature is the presence of focal areas of calcification of the cellular tumor tissue. Multinucleated giant cells and basic polyhedral cells or round cells with fairly large nuclei were found. The lesion is benign and heals without recurrence after curettage, even without supplementary irradiation. The tumor should not be regarded as a giant cell variant, since the tumor cells are chondroblasts and the tumor is a benign chondroblastoma.

Gold¹⁸⁹ reports a case of extraosseous and apparently extrabursal chondroma of the big toe of the left foot. The patient was a man 42 years of age. Excision of the tumor was performed without wide resection, and no recurrence had taken place within a year. The author suggests that these tumors can be considered benign with reasonable certainty. Stabler¹⁹⁰ reports 2 cases of enchondroma. In 1 the tumor was asymptomatic and operation was not performed. In the other the tumor was curetted and was found to be a chondroma. He emphasizes that operation is not necessary if one is certain of the diagnosis.

[ED. NOTE.—Chondromatous tumors tend to recur unless thoroughly removed. Microscopically, they are often benign, but grossly they react as locally malignant lesions; that is, they recur and may attain such size that they are inoperable.]

Giant Cell Tumors.—Benign Giant Cell Tumors: Garber¹⁹¹ classifies cystic disease of bone as follows: (1) solitary bone cyst; (2) acute polycystic bone cyst; (3) multiple osteitis fibrosa cystica (von Recklinghausen) and (4) benign giant cell tumor. He emphasizes that this is a disease of adults which usually appears in the epiphyses and is usually preceded by trauma and by pain and swelling. As a rule, no periosteal reaction is seen on roentgenologic study. The gross lesion generally is hemorrhagic and friable. Microscopic examination reveals fibrous proliferation and formation of new bone. Giant cells with 15 to 200 nuclei and stromal round cells and spindle cells are present. Changes in blood supply to bone following trauma and resultant upset in the osteoclastic activity were emphasized

188. Jaffe, H. L., and Lichtenstein, L.: Benign Chondroblastoma of Bone: A Reinterpretation of the So-Called Calcifying or Chondromatous Giant Cell Tumor, *Am. J. Path.* **18**:969-991 (Nov.) 1942.

189. Gold, A. M.: Extra-Osseous Chondroma of the Foot: Case Report, *Bull. Hosp. Joint Dis.* **3**:134-140 (Oct.) 1942.

190. Stabler, F.: Degenerate Enchondroma of the Femur and Tibia, *Brit. J. Radiol.* **15**:269-271 (Sept.) 1942.

191. Garber, J. N.: Giant Cell Tumors of Bone, *Quart. Bull. Indiana Univ. M. Center* **4**:10-14 (Jan.) 1942.

as etiologic factors. There is a tendency for recurrence after apparent eradication. The authors feels that the best form of treatment is curettage and cauterization and filling of the cavity with bone chips.

A Cabot case¹⁹² is reported in which the patient, a man 35 years of age, had had disability of the right elbow for one month. He had received a blow on the elbow one year previously and had had occasional pain in the elbow since. There was limitation of extension of a few degrees. Roentgenograms revealed a multilocular cystic area in the medial epicondyle of the humerus. At operation, the cavity was found to contain yellowish and pinkish friable material. Curettage was performed and the cavity allowed to remain empty. Microscopic examination revealed a benign giant cell tumor. The patient was observed for two and a half years and received three courses of roentgen therapy. There was some question of enlargement recurring, and the flexion deformity increased. The tumor was removed, and arthrodesis of the ulnohumeral joint was performed. The patient was a laborer and needed a stable, painless joint.

Kaplan¹⁹³ reports a case of giant cell tumor of the vertebra with hemorrhage into the neoplasm and resulting acute compression of the spinal cord. The patient was a woman 22 years of age. Recovery followed excision of the tumor. He also reports a case of hemangioendothelioma of the vertebra with hemorrhage into the tumor and acute compression of the spinal cord. The patient was a woman 44 years of age. Recovery followed excision of the tumor. He stresses the importance of early recognition of the acute compression of the spinal cord and its immediate surgical relief.

Malignant Giant Cell Sarcoma: "Atypical giant cell tumor" is interestingly described by Coley and Miller¹⁹⁴:

The typical giant cell tumor is well recognized as a lesion which, while benign, is locally invasive and may recur after treatment. Its most frequent site is the epiphyseometaphyseal regions, with extension in advanced cases into the adjacent diaphysis. Save for rare exceptions, the lesion is subcortical in origin and tends to destroy the cancellous cortical bone. As it progresses, the cortex is reduced to a thin shell or may disappear entirely, although the periosteum remains as a limiting membrane offering resistance to extension into the overlying soft parts.

Distinctly atypical cases are rarely encountered. However, the importance of recognizing them is obvious, for unless their nature is appreciated, the proper treatment cannot be carried out.

The atypical cases may be divided into two groups: (1) atypical because of clinical and pathologic criteria, and (2) atypical because of location.

In the first group are those giant cell tumors that are malignant at the time of first observation, the diagnosis being based on study of tissue removed prior to the administration of any form of treatment; and also those tumors that are believed to have undergone a malignant transformation following unsuccessful treatment, i. e., curettage, irradiation, or both.

In the second group is found that rare example of an expanding osteolytic lesion involving the shaft of a long bone rather than the extremity. The roentgenographic appearance does not simulate that of a malignant tumor, although, from its location, a benign giant cell tumor is not suspected. Under conservative surgery or irradiation this lesion responds in the manner of a giant cell tumor, and sections of tissue are so diagnosed by the pathologist, although, in some instances, a report of "angioma of bone" may be returned. In these cases, there may be reactive hyperplasia with fibrosis and giant cell areas.

192. Giant Cell Tumor of Humerus, Cabot Case 28141, *New England J. Med.* **226**: 571 (April 2) 1942.

193. Kaplan, A.: Acute Spinal Cord Compression Following Hemorrhage Within Extradural Neoplasm: Report of Two Cases with Recovery, *Am. J. Surg.* **57**:450-456 (Sept.) 1942.

194. Coley, B. L., and Miller, L. E.: Atypical Giant Cell Tumor, *Am. J. Roentgenol.* **47**:541-548 (April) 1942.

As to the importance of these atypical giant cell tumors, it is obvious that those that are malignant from the outset should be recognized and treated as malignant tumors. This implies the use of radical surgery with or without preliminary irradiation.

In the more frequently observed examples of malignant transformation of a benign tumor, the factors that have led to such alteration of growth deserve a careful consideration. It must be acknowledged that a completely satisfactory explanation of the cause or causes of this alteration has never been offered. In collaboration with Stewart and Farrow the records of the Memorial Hospital and the Hospital for Ruptured and Crippled were reviewed and found to contain 7 unquestionable examples of such malignant transformation of a previously benign giant cell tumor.

Where the tumor occupies an atypical location, it is essential that its benign nature be recognized so that conservative treatment can be employed. In one such case personally observed, a recurrence took place after biopsy and incomplete removal; irradiation, however, yielded an excellent result. It seems not unlikely that, in the past, amputation may have been performed for such tumors under the mistaken impression that the lesion was an osteogenic sarcoma of osteolytic origin.

The following quotation has been taken from an article on primary malignant giant cell sarcoma of long bones by Meyerding and Broders¹⁹⁵:

We wish to report a series of seven cases of tumor of the long bones in which the lesion was recognized as malignant at the time of operation and which, following recent microscopic study, we have classified as primary malignant giant-cell sarcoma. While there may be objections to the use of the term, "primary malignant giant-cell sarcoma," we have used it here in the sense that the giant-cell tumor was malignant at the time of the first microscopic examination. This group of tumors does not include those benign foreign body giant-cell tumors which were recognized originally as benign and which subsequently underwent a malignant transformation. Furthermore, we recognize a rare osteogenic type of sarcoma which may contain numerous foreign body giant cells that mask its true malignant nature.

The lesions in the seven cases herein reported are giant-cell tumors which apparently show primary malignant changes in the stroma and are here designated "primary malignant giant-cell sarcomas." In six cases the lesion occurred in both epiphyses and the lower part of the femur and in one case in the upper epiphysis and the upper part of the diaphysis of the tibia; all, therefore, occurred at the knee joint. In no case did we encounter malignant giant cells as the malignancy was always found in the tissue between the foreign body giant cells. Three of these patients have died, one within three months, one within five months, and one three years and seven months after treatment; one of these three had biopsy and irradiation and two had amputation and irradiation. The remaining four patients are still living, one four years, one ten years, one twelve years and one fifteen years after treatment; all of these four patients had amputation and irradiation.

Amputation following early diagnosis and pathologic proof of malignancy is the treatment of choice in cases of this type.

Vascular Tumors.—Thomas¹⁹⁶ reports the results of a pathologic and clinical study of 27 cases of vascular tumor of bone from the Registry of Bone Sarcoma. There are several reasons why there has been confusion regarding vascular tumors. Histologists and pathologists have not agreed as to what should be called endothelium. The reason for this is that in the adult form it is often impossible to distinguish squamous areas of mesenchymal cells (endothelium) from those of ectodermal or entodermal origin. Adult cells similar in structure and arrangement may have a totally different embryonic origin and quite different developmental potentialities. For this reason attempts to identify and classify neoplasms of the so-called endothelial group have proved difficult and controversial. A simple and workable classification is one which considers vascular tumors as endotheliomas accompanied by a very definite vasoformative tendency with endothelial proliferation and formation of new blood vessels. The tumors may be classified as (1) benign

195. Meyerding, H. W. and Broders, A. C.: Primary Malignant Giant-Cell Sarcoma of Long Bones, *Tr. West. S. A.* (1941) 51:76-95, 1942.

196. Thomas, A.: Vascular Tumors of Bone: A Pathologic and Clinical Study of Twenty-Seven Cases, *Surg., Gynec. & Obst.* 74:777-795 (April) 1942.

angioma, a slowly growing, highly differentiated tumor, congenital in origin, with definite well formed blood vessels and an innate tendency to regress and heal, and (2) malignant angioma, a more cellular and compact growth, with active endothelial proliferation and invasiveness, which shows a tendency to revert to its primitive mesenchymal structure. In certain cases of malignant angioma it is possible to identify two subdivisions, namely angioendothelioma and angiosarcoma. The angioendothelioma shows a rather marked cellular proliferation, and as it has a tendency to revert to a primitive mesenchymal structure the cells assume a cuboidal appearance and alveolar arrangement closely resembling those of epithelial tissue. Nevertheless formation of new blood vessels is evident. In angiosarcoma the vasoformative tendency is much more prominent. This formation of new vessels is the predominant feature of the tumor and enables it to be more easily identified as a true vascular tumor.

In the 12 cases of benign angioma 6 of the patients were males and 6 were females. The ages of the patients ranged from 15 to 62 years. The vertebrae probably formed the most common site of involvement. The treatment consisted of irradiation or operation or both. The author quotes Meyerding as stating that he found angioma of bone to be somewhat radiosensitive and that the use of moderate doses repeated at regular intervals for a number of months caused it to regress gradually and to heal.

In the 15 cases of malignant angioma 8 of the patients were males and 7 were females. The ages of the patients ranged from 3 to 53 years. In the majority of cases the tumor occurred during the second and third decades of life. The long bones were the ones most frequently involved. Multiplicity of the lesion was found in 6 cases. Amputation was performed in 9 cases, with apparent cure in 4. In 1 case the operation had been performed recently. Exploration and curettement were performed in 1 case, and there was no recurrence in more than ten years. Irradiation was employed in 10 cases; death occurred in 6 of these. The 4 surviving patients were treated by irradiation and amputation.

[ED. NOTE.—This is an interesting and informative article written on this rather rare condition and supplies a very good résumé of the literature on the subject.]

Ackermann and Hart¹⁹⁷ report a case of primary hemangioma of the bones of the extremity and state that a survey of the literature revealed it to be the sixteenth such case on record. Their patient was a white boy 15 years of age, whose chief complaint was progressive, painless swelling of the left ankle and knee of four years' duration. Eighteen months prior to his admission he had injured his ankle and had used crutches. Examination revealed a uniform enlargement of the ankle and a fusiform swelling of the left leg just below the knee, which were not tender. Roentgenographic examination revealed multiple hemangioma of the proximal and distal ends of the shaft of the tibia and proximal end of the shaft of the fibula. Microscopic examination of the specimen removed from the distal end of the shaft of the tibia revealed hemangioma. In 1940, or ten years after the patient's first examination, the roentgenogram also showed involvement of the bones of the foot. The gross pathologic examination showed that no bone was exempt. There were gross uniform expansion of bone and multiple cystic cavities of various size which were filled with bloody fluid. Microscopic examination revealed the usual cavernous type of hemangioma with large irregular endothelium-lined spaces filled with erythrocytes. The cavernous spaces were separated by compact fibrous tissue. Roentgenographic examination revealed fusiform enlargement of the epiphysal ends of the bones or of the segments close to the nutrient artery. The tumor was

197. Ackermann, A. J., and Hart, M. S.: Multiple Primary Hemangioma of the Bones of the Extremity, *Am. J. Roentgenol.* 48:47-52 (July) 1942.

central in origin; as it enlarged, it caused the bone to expand. The medullary border of the cortex was usually irregular. The bone trabeculae within the tumor were coarse and denser than the normal cancellous bone. The involved bone was often loculated. The periosteum remained intact. The tumor did not involve the epiphysal cartilage and had not penetrated into the joints. The treatment of choice is irradiation.

Kleinberg¹⁹⁸ reports a case in which angioma involved the cuboid bone, the external cuneiform bones and the soft tissue of the foot. The patient was a girl 19 years of age. She had had intermittent limp for eleven years and had had occasional pain and disability. There was a tender mass on the plantar surface of the foot. Excision of the tumor and the subsequent use of roentgen therapy produced a good result.

Malignant Hemangioendothelioma: Aitken¹⁹⁹ presents a concise and thorough summary of the confused state existing regarding Ewing's sarcoma, clinically as well as histologically. He expresses the opinion that it is a rarity and that there is lack of uniformity as to the constitution of the lesion. He says that the diagnosis never can be accepted until there is gross, histologic and postmortem proof of the true nature of the lesion, since clinically it can be simulated by numerous other malignant as well as benign lesions. The author reports a case in which the clinical features and biopsy indicated Ewing's sarcoma of bone, whereas necropsy revealed a primary adrenal neuroblastoma and metastatic involvement of bone. The patient was a girl 16 years of age. She had had intermittent pain in the lower part of the leg for six months, but there was no history of trauma. The temperature and pulse rate were normal. There was slight swelling at the middle third of the right tibia, which was hot and slightly red. Nothing else of significance was found. Roentgenograms of the tibia revealed a diffuse osteoplastic process with some subperiosteal formation of bone of parallel type. Roentgenologic examination of the thorax did not disclose any abnormality.

Local roentgen irradiation was instituted after biopsy, and although 3,264 r was given, subsequent roentgenographic study of the tibia showed no change in the bone. Later, because of drowsiness, irritability and vomiting, a roentgenologic study of the skull was made. The appearance was similar to that seen in cases of increased intracranial pressure. Craniotomy disclosed an extradural mass, which was a highly cellular malignant tumor. Irradiation was applied again to the right tibia and to the skull. A second roentgenographic study showed no significant changes in the bone after this course of treatment. The patient's condition became progressively worse, and death occurred.

Necropsy revealed an ill defined retroperitoneal tumor, metastatic involvement of the mandible, early deposits in the shafts of both humeri and some secondary deposits in both the lungs and the pleura and in the lymph nodes of the thorax. Generally, all signs, symptoms and laboratory findings were commensurate with a diagnosis of Ewing's tumor up to the time of the necropsy.

[ED. NOTE.—In many publications one of the editors (H. W. M.) has emphasized that the true nature of this lesion may not be determined until pulmonary metastasis occurs, or until necropsy.]

Heiligman²⁰⁰ reports a case of sarcoma of the femur in which the patient was a white boy 19 years of age. Death occurred in twelve months as a result of

198. Kleinberg, S.: Angioma of Foot, *J. Bone & Joint Surg.* **24**:367-371 (April) 1942

199. Aitken, S. G.: Metastatic Neuroblastoma in Bone, *New Zealand M. J.* **41**:200-212 (Oct.) 1942.

200. Heiligman, R.: Atypical Ewing Tumor: Problem in Diagnosis, *Bull. Hosp. Joint Dis.* **3**:41-46 (Jan.) 1942.

multiple metastatic involvement. Disarticulation at the hip was performed after a needle biopsy and subsequent incision biopsy. The pathologic report was of malignant tumor. Necropsy revealed that metastasis had occurred and involved the spinal cord, the ribs, the sternum, the pelvis and the skull. The intermittent symptoms and history pointed to Ewing's sarcoma.

Barden, Belk, Pratt and Taylor²⁰¹ report a case in which the patient was a boy aged 5 years. He was seen in February 1940. There was a history of intermittent pain and fever. Pain was situated in the lower part of the right leg and knee, and swelling and tenderness were present. The symptoms were migratory and simulated those of acute articular rheumatism (other points of involvement were the knees, ankles and elbows). Tenderness along the shafts of the adjacent long bones was noted, and cardiac symptoms were present. Roentgenographic examination revealed punched-out areas in the skull, the pelvis and the diaphyses of the femurs and tibiae and typical proliferation along the shafts of the long bones. Supportive therapy and roentgen therapy for relief of pain in the bones and joints were instituted. The patient failed gradually and died about eight months after his admission to the hospital and fifteen months after onset of symptoms. Biopsy revealed a collection of large, pale cells with densely chromatic nuclei. The cells were arranged in pavement fashion and corresponded to the cells of Ewing's sarcoma (endothelial myeloma).

Sloat and Peterson²⁰² report a case of Ewing's tumor of the sacrum in which the patient was well five years after the diagnosis was made by biopsy. Intensive roentgen therapy was employed. This consisted of courses of 7,000 r, 4,611 r and 2,522 r.

Adamantinoma.—Dockerty and Meyerding²⁰³ report 2 cases of adamantinoma of the tibia and state that extracranial adamantinomas are rare neoplasms that occur in bones (tibia and ulna) in which a sharp ridge of osseous tissue closely approximates the overlying skin. Prior to 1942, 15 cases of this tumor had been reported.

In the first case reported by these authors the patient was a pregnant woman 24 years of age, who complained of intermittent pain of eight years' duration and a "lump" which had been present on the left shin for fifteen months. Roentgenograms had been interpreted as indicating an atypical giant cell tumor, and biopsy had suggested a metastatic malignant process. Amputation was performed for a large adamantinoma.

[ED. NOTE.—One year later metastasis appeared in the inguinal lymph nodes, and death occurred shortly thereafter.]

In the second case the patient was a man 27 years of age, who had noticed the tumor following a "shearing" type of trauma of the left tibia which had occurred at the age of 10 years. One pathologic fracture had occurred. After several operations the growth apparently was successfully removed.

The site of the lesions combined with the frequent history of injury suggests that local trauma may play some part in the production of tibial adamantinoma. The tumor is of slow evolution but is so invasive that amputation of the leg almost always becomes necessary. Metastasis is possible. Roentgenologically, the appearance suggests a giant cell tumor, but invasion of soft parts indicates atypical (malignant) characteristics. Microscopically, the lesion is liable to be mistaken for

201. Barden, R. P.; Belk, W. P.; Pratt, G. E., and Taylor, W. R.: Ewing's Endothelial Myeloma with Extensive Skeletal Involvement, *Radiology* **39**:334-336 (Sept.) 1942.

202. Sloat, J. I., and Peterson, L. T.: Ewing's Tumor of the Sacrum, *J. A. M. A.* **119**: 1499-1500 (Aug. 29) 1942.

203. Dockerty, M. B., and Meyerding, H. W.: Adamantinoma of the Tibia: Report of Two New Cases, *J. A. M. A.* **119**:932-937 (July 18) 1942.

metastatic carcinoma. The cellular pattern varies from that of a basal cell or squamous cell carcinoma to an adenocarcinoma. Intermediate histologic pictures in which the cells resemble ameloblasts have been responsible for the use of the term "adamantinoma." The authors concur in the belief that tibial adamantinomas arise from the basal layers of the overlying skin and that the bone "tumor" accordingly represents secondary invasion. In 1 of their cases there was evidence of such a primary cutaneous malignant process.

Bell²⁰⁴ reports a case of adamantinoma of the femur and mentions the comparative frequency of this lesion in the jaws. His case is the first one of adamantinoma of the femur that has been reported. The patient was a native African 16 years of age. He complained of pain in the left knee, aggravated by motion, and of a swelling of the lower end of the femur. The temperature ranged from 98 to 100 F. A diagnosis of deep abscess was made. An exploratory incision did not disclose any pus; instead, there was a fleshy growth, which was incised. The femur contained bony spicules and irregular masses. The patient died five weeks later. Microscopic examination revealed cellular strands in a vascular fibrous stroma. The cells were spindle shaped or stellate, with a surrounding layer of high columnar epithelium.

Anderson and Saunders²⁰⁵ report a case of adamantinoma of the ulna in which the patient was a man 49 years of age, who had sustained fractures of the right arm above the wrist in 1902 and 1905. In 1929 there was a palpable dislocation of the head of the radius with limitation of supination and diffuse swelling over the ulnar side of the forearm. Roentgenographic examination revealed a rarefying process which extended to within an inch (2.5 cm.) of either end of the ulna. The distal part of the cortex was thin and contained large round and smaller foamlike lobules; the remainder of the involved region had a more dense appearance with honey-combed trabeculae. The lower portion of the shaft of the ulna was resected and a tibial graft inserted. Good recovery occurred, and the patient was free of symptoms for four years. Weakness and paresthesia of the right arm then recurred. Roentgenographic examination at this time showed that the disease had involved the ulna and the bone graft. Temporary relief of pain followed the use of roentgen therapy. The values for calcium, phosphorus and phosphatase in the serum were normal. One month later roentgenographic examination showed complete absence of bony cortex over the tumor and extension of the tumor into the soft tissues. An attempt was made to resect the ulna and the tumor, but this was impossible and part of the tumor remained. Pain recurred two months later, and amputation was performed through the lower portion of the humerus. The patient had remained in excellent health without evidence of recurrence or metastasis for six years.

The tumor was an infiltrating epithelial type of lesion. It originated from the basal cells that grew in fibrous tissue stroma. It had, to a certain extent, the histologic characteristics of a tooth bud.

Fischer, in 1913, expressed the opinion that this type of tumor arises from cell rests. Ryrie, in 1932, said that such tumors arise from basal cells implanted in the deeper structures by trauma, and Anderson and Saunders agree with this opinion.

The tumor is a soft, spongy, gray, indistinctly lobulated vascular growth which occupies the central portion of the shaft of the bone and expands it without breaking through the cortex. Microscopically, it is an infiltrating epithelial tumor in a stroma of fibrous tissue.

204. Bell, A. L.: A Case of Adamantinoma of the Femur, *Brit. J. Surg.* **30**:81-82 (July) 1942.

205. Anderson, C. E., and Saunders, J. B. de C. M.: Primary Adamantinoma of the Ulna, *Surg., Gynec. & Obst.* **75**:351-356 (Sept.) 1942

The tumor is of a low grade of malignancy and does not metastasize. It affects both sexes, and the ages of the patients range from 22 to 46 years. In Bell's case²⁰⁴ the tumor occurred in an African boy who was 16 years of age. In all the cases reported in the literature there was a history of trauma which was not as severe as a fracture. The first symptom usually is a mass.

Roentgenographic examination reveals a polycystic, expanding central tumor with a sharp outline and a fine trabecular pattern. There is no periosteal reaction. The tumor may be finely honeycombed.

Treatment consists of complete excision of the tumor, resection of the involved bone or amputation of the affected limb. Radiosensitivity of the tumor is low, and there is a tendency for it to recur if it is not completely removed.

Tumors of the Spinal Canal.—French and Peyton²⁰⁶ report 3 cases of proved mixed tumor (teratoma) of the spinal canal. In all 3 cases there was a characteristic history of symptoms of long duration before the patient became incapacitated, and there was roentgenologic evidence of fusiform enlargement of the spinal canal and of spina bifida. When the interpedicular distance of a spinal canal is larger than normal (or an increase of 2 to 4 mm. is present in consecutive vertebrae), this evidence is consistent with a diagnosis of mixed tumor. The authors have noted that a similar chronicity of symptoms and similar roentgenologic changes are present in cases of lipoma. They say that roentgenologic examination produces evidence of fusiform pressure erosion over several vertebrae. The first sign is thinning of the lamina and narrowing of the pedicles, with a resulting increase in the distances between the pedicles; later, there is erosion of the posterior surfaces of the bodies of the vertebrae.

In discussing tumors simulating protrusion of an intervertebral disk, Nosik²⁰⁷ reports 3 cases of pain low in the back with sciatica in which there was a textbook picture of protrusion of an intervertebral disk. Laminectomy revealed melanoma, neurofibroma and plasma cell myeloma. He stressed the fact that at this time, when protruded disk has been brought to the front in diagnosis, it is easy to overlook the fact that other, rarer lesions can and do produce symptoms identical with those of protrusion of an intervertebral disk.

Conley and Miller²⁰⁸ report a case of neurilemmoma of the first sacral vertebra in which the patient was a woman 32 years of age. The symptoms consisted of pain along the left sciatic nerve, which began in 1928. The patient was seen in 1939, at which time examination revealed atrophy of the left thigh and calf, a limp and a steppage gait. There were definite reflex and sensory changes in the left leg. Roentgenographic examination revealed rarefaction of the left side of the body of the first sacral vertebra. Operation consisted of exposure and curettage of the cystlike cavity. Roentgen therapy was given weekly for ten weeks, and the patient remained under observation for three years. Serial roentgenograms revealed bony replacement in the cavity. The pain was relieved, and sensation returned. The original atrophy remained. The tumor consisted of palisaded nuclei and loose connective tissue stroma.

Siris and Angrist²⁰⁹ report a case of chondroblastic meningioma in which the patient was a boy 18 years of age. This is the twenty-sixth case of this type

206. French, L. A., and Peyton, W. T.: Mixed Tumors of the Spinal Canal, *Arch. Neurol. & Psychiat.* **47**:737-751 (May) 1942.

207. Nosik, W. A.: Unusual Tumors Simulating Protrusion of the Intervertebral Disc, *Cleveland Clin. Quart.* **9**:54-59 (Jan.) 1942.

208. Conley, A. H., and Miller, D. S.: Neurilemmoma of Bone, *J. Bone & Joint Surg.* **24**:684-689 (July) 1942.

209. Siris, J. H., and Angrist, A.: Chondroblastic Meningiomas, *Am. J. Surg.* **57**:162-167 (July) 1942.

reported in the literature, and the sixth one in which all of the tumor was removed successfully. There is much speculation as to the site of origin of this tumor. The authors suggest that it possibly may originate from cartilaginous rests misplaced during development of the skull. Transition of meningeal fibroblasts to cartilage cells was mentioned. Another theory is that it may originate from cell rests in the arachnoidal granulations. There are no pathognomonic symptoms or signs. The prognosis is relatively favorable if the tumor is completely excised.

Experimental Work on Diagnosis of Tumors of Bone.—Inclan²¹⁰ has used arteriography to diagnose malignant tumors of bone and also has carried out experiments by using different kinds of opaque substances. He expresses the opinion that this method affords an earlier diagnosis of tumors of bone. If the tumor is still limited to bone and if no invasion of soft tissue is yet evident, surgical block excision may be adequate, and in those cases in which amputation is refused this procedure at least offers a possibility of doing something for the patient. The most striking characteristic arteriographic sign of malignant disease of bone is the filling in of the stroma of the new growth by numerous vessels, showing extension of the invading tumor. A second evidence is the presence of new, atypical arterial circulation with pedicles from the main artery and numerous irregular branches entering the bone lesion. Inclan enumerates the objections to this method of diagnosing tumors of bone, but none of them, he says, are sufficient to condemn a procedure which makes possible a positive and early diagnosis of malignant tumors of bone. In addition to the methods previously described for this procedure, he advocates a new technic, which consists of ascending instillation of the opaque substance. He expresses the opinion that this technic will be of value in those cases in which descending arteriography would be either impractical or impossible. He says that the procedure deserves further trial, especially in institutions devoted to the study of cancer, where the real value of the procedure may be ascertained.

Treadwell, Low-Beer, Friedell and Lawrence²¹¹ in their report on "Metabolic Studies on Neoplasm of Bone with the Aid of Radioactive Strontium" state that, experimentally, calcium and strontium have a selective localization in bone. The application of the radioactive isotopes of these substances to clinical metabolic studies and possibly to therapeutic irradiation of bone seemed feasible. The value for serum phosphatase was lowered in those cases of carcinoma of the prostate in which the lesion had metastasized to bone. In 6 cases of tumor of bone they have given radioactive strontium prior to biopsy or amputation, and by postoperative studies of the specimen they have found that the strontium had been taken up chiefly by growing bone and by osteogenic tumor tissue. They express the opinion that various considerations seem to justify the therapeutic use of radioactive strontium in certain cases of tumor of bone.

Treatment of Tumors of Bone.—Copeland²¹² says that a bitter lesson has been learned in radiotherapy of tumors of bone, namely, that radiosensitivity does not parallel radiocurability. He says that osteochondroma that occurs singly is curable by surgical excision. He has observed malignant change in a few cases in which multiple osteochondromas were present. Roentgen rays and radium play a slight role in the treatment of this type of tumor.

210. Inclan, A.: The Possibilities of Roentgenographic Study of the Arterial Circulation in the Early Diagnosis of Bone Malignancy, *J. Bone & Joint Surg.* **24**:259-269 (April) 1942

211. Treadwell, A. de G.; Low-Beer, B. V. A.; Friedell, H. L., and Lawrence, J. H. Metabolic Studies on Neoplasm of Bone with the Aid of Radioactive Strontium, *Am. J. M. Sc.* **204**:521-530 (Oct.) 1942.

212. Copeland, M. M.: Bone Tumors with Reference to Their Treatment, *Surgery* **11**: 436-455 (March) 1942.

In cases of chondroma, Copeland says that the site of the tumor is of importance. When the small bones of the hand or foot are involved, the lesion usually is benign, and curettage and excision are advisable. When the tumor involves the sternum, the spinal column, or the long bones, the lesion must be considered as potentially malignant. Surgical treatment and roentgen therapy are advisable in the treatment of this type of tumor, as it is radioresistant.

He feels that primary chondromyxosarcoma usually affects patients who are 14 to 21 years of age. He says that it commonly is situated about the knee, shoulder and pelvic girdle. A subperiosteal shadow streaked with calcium spicules is visible in the roentgenogram. Permanent cure was obtained in 9 per cent of his series of cases. Irradiation relieved pain but was not curative. Amputation was performed in 3 of 5 cases.

Chondrosarcoma may occur as a secondary lesion in cases in which the patients have had chondroma, osteochondroma, osteitis deformans (Paget's disease) or hereditary chondrodysplasia. The bones most frequently involved are the ribs, the femur, the heel bone and the humerus. Roentgenographically the tumor appears as a fuzzy periosteal shadow flecked with calcium. A pathologic fracture may occur. In 18, or 26 per cent, of the cases of chondrosarcoma the patients were living five or more years after operation. Amputation of the affected limb was performed in 8 of these cases; in the remaining 10 a combination of roentgen therapy and surgical treatment was employed.

Copeland expresses the opinion that osteoblastic osteogenic sarcoma usually affects persons between 15 and 25 years of age. He says that the lesion usually is situated in the lower portion of the femur or in the upper part of the tibia. The roentgenographic appearance consists of dense radiating ("sun-ray") shadows and evidence of new bone in the periosteal zone. Later in the course of the disease the medullary cavity is obliterated. In 26 per cent of his cases the patients obtained a cure after amputation or irradiation or a combination of the two.

There has been a trend toward increased conservatism in the treatment of benign giant cell tumor. Copeland says that curettage and cauterization are indicated when the lesion has not reached an advanced stage and that resection and irradiation may be employed in selected cases in which the lesion is advanced. He feels, however, that patients with certain lesions treated by irradiation alone, or by surgical excision alone, obtain a cure, but that unfortunate results may accrue from such a combination. Irradiation employed preoperatively or postoperatively is of little value in the treatment of this lesion.

Chondroblastic sarcoma is a rare osteolytic variant of osteogenic sarcoma. Copeland says that this tumor is most effectively treated by large doses of roentgen rays or radium. Osteolytic osteogenic sarcoma, as shown in roentgenograms, causes bone cells to melt away; it is eccentrically situated. It is not radiosensitive and does not respond to therapeutic doses of roentgen rays or radium. Amputation produced a five year survival rate of 10 per cent in Copeland's series of cases.

Hemangioendothelioma (Ewing's sarcoma or tumor) may be therapeutically tested by irradiation, which also produces the best palliative result. Copeland says that the best five year survival rate can be obtained with preoperative irradiation and radical excision or amputation. Multiple myeloma may be treated palliatively by means of irradiation with roentgen rays or radium, which relieves pain and produces temporary symptomatic improvement.

Fibrosarcoma may be of periosteal or neurogenic origin. The first type has a low grade of malignancy and is highly radiosensitive. Amputation or radical resection results in a cure in the majority of instances. However, the undifferentiated,

oat-cell type of fibrosarcoma does not respond to conservative treatment, and primary amputation is the treatment of choice. Clinical cure of neurogenic sarcoma may be obtained by surgical intervention. Amputation gives the best result, but a permanent cure seldom is obtained.

Angioma of bone is rare and essentially benign. Radiosensitiveness of this tumor varies. Myositis ossificans may be best treated by conservative methods, but therapeutic doses of roentgen rays may be of value in a few cases. The lesions of Hand-Schüller-Christian disease are radiosensitive, and transfusion frequently is indicated.

Higinbotham and Coley²¹³ in their discussion of osteogenic sarcoma state that the five year survival rate is as follows: 8.5 per cent in cases in which only irradiation is used, 31 per cent in cases in which operation is employed and 34 per cent in cases in which both types of treatment are employed. As a result of a study of 114 cases of osteogenic sarcoma in the past five years, they advise delivering at least 4,000 r to all parts of the tumor and then performing a radical amputation as soon as the skin is healthy enough. The irradiation of each tumor should be planned individually. Its efficacy varies with the different types of osteogenic sarcoma; satisfactory effects are evidenced by a lowering of the value for the serum phosphatase if it was elevated previously. Pain is partially or entirely alleviated. They emphasize that the condition of the skin must be carefully watched. Postamputation irradiation is seldom if ever indicated.

Valls²¹⁴ in an article entitled "Osteogenic Sarcoma (Malignant Osteoblastoma, Brachetto-Brian)" exhaustively reviews the literature and submits the term "malignant osteoblastoma" for use in classifying malignant tumors of bone which arise from cells of the osteoblastic or potential bone-forming type but which do not necessarily form bone in the mass. He stresses the inability of roentgenographic examination or of clinical study alone to reveal the type of bone tumor and the need of cooperation of all branches of science in diagnosis and treatment. He considers surgical intervention of prime importance in treatment and roentgen therapy as an adjunct.

Hansen²¹⁵ reports a case in which a diagnosis of osteitis deformans had been made when the patient, a man 52 years of age, had fractured his right humerus. After he had worn a cast for six weeks, swelling and burning were noticed and roentgenologic examination revealed destruction of bone. A diagnosis of sarcoma was made. Amputation was at first refused; therefore roentgen therapy was employed. Later, amputation was done for relief of pain. The patient died soon after the operation, and permission for necropsy was not obtained.

Atsatt²¹⁶ reports a case of osteogenic sarcoma in which the patient, a cowboy 29 years of age, first reported for examination eleven months after an accident. Five months later, a section of the fibula was removed. Six months later, the recurrent tumor attained considerable size and amputation was performed at the middle of the thigh. Kirkman²¹⁷ reports an instance of this type of lesion in

213. Higinbotham, N. L., and Coley, B. L.: The Methods and Effects of Preoperative Irradiation in the Treatment of Osteogenic Sarcoma, *Am. J. Roentgenol.* **47**:902-908 (June) 1942.

214. Valls, J. E.: Osteogenic Sarcoma (Malignant Osteoblastoma, Brachetto-Brian), *Rev. ortop. y traumatol.* **11**:291 (April) 1942; **12**:48 (July) 1942.

215. Hansen, T. L.: Sarcoma as Complication to Paget's Disease, *Tr. West. S. A.* (1941) **51**:59-75, 1942.

216. Atsatt, R. F.: Osteogenic Sarcoma as Concomitant of Industrial Accident, *Am. J. Surg.* **57**:143-146 (July) 1942.

217. Kirkman, J. H.: Osteogenic Sarcoma Following Open Reduction for Fracture of Humerus, *M. Bull. Vet. Admin.* **18**:436-437 (April) 1942.

the humerus. The tumor occurred after open reduction and the use of a beef bone-dowel pin; no union was secured at the site of the fracture. Amputation was performed eleven months after the first operation. Atsatt mentioned reports of cases in which sarcoma occurred after open reduction of fractures.

Pack and Braund²¹⁸ reviewed the literature on myositis ossificans and found 5 cases in which a malignant neoplastic change of the bony tissue had occurred as a complication of this disease. In 4 of these 5 cases an osteogenic sarcoma occurred as a complication of myositis ossificans traumatica, and in 1 case a sarcoma occurred in a calcified hematoma. They report 3 cases of this complication. In 2 of these cases the sarcoma occurred in preexisting myositis ossificans conscripta, and in the remaining case myositis ossificans progressiva was associated with a malignant tumor, probably a myxoliposarcoma.

Sullivan²¹⁹ found reports of about 30 cases of osteosarcoma and chondrosarcoma of the breast, but only 7 or 8 cases of osteochondrosarcoma. He feels that in the majority of cases the exciting agent apparently was trauma. All of the patients were beyond the third decade of life. He reports 1 case in which osteochondrosarcoma followed a severe contusion of the breast.

Geschickter,²²⁰ in an article entitled "Neoplastic and Related Conditions in the Bones of Children," recommends the following simple classification of bone lesions which affect children:

- I. Inflammatory
- II. Metabolic
- III. Neoplastic
 - Benign
 - Osteochondroma
 - Chondroma
 - Bone cyst
 - Malignant
 - Primary—Ewing's sarcoma, osteogenic sarcoma
 - Secondary—metastatic

He emphasizes the diagnostic use of roentgen rays in cases of Ewing's sarcoma and says that resection or amputation should be performed after the maximal effect of these rays has been achieved. If resection or amputation is not feasible, subsequent courses of roentgen therapy are given. He says that roentgen therapy alone is never curative in cases of Ewing's sarcoma.

Bassas Grau²²¹ reports a case of von Recklinghausen's disease in which sarcomatous degeneration occurred as a result of surgical trauma. Caeiro, Zanchi and Bonduel²²² report a case of traumatic sarcoma of the tibial tuberosity.

218. Pack, G. T., and Braund, R. R.: The Development of Sarcoma in Myositis Ossificans, *J. A. M. A.* **119**:776-779 (July 4) 1942.

219. Sullivan, S. J.: Osteochondrosarcoma of the Breast, *Illinois M. J.* **82**:140-141 (Aug.) 1942.

220. Geschickter, C. F.: Neoplastic and Related Conditions in the Bones of Children, *Rhode Island M. J.* **25**:98-101 (May) 1942.

221. Bassas Grau, E.: Sarcomatous Degeneration in Recklinghausen's Disease, *Actas dermo-sif.* **33**:368-371 (Jan.) 1942.

222. Caeiro, J. A.; Zanchi, A., and Bonduel, A.: Sarcoma of Traumatic Origin, *Rev. Asoc. méd. argent.* **56**:153-155 (March 15-30) 1942.

HISTOMECHANICAL ANALYSIS OF NERVE REUNION IN THE RAT AFTER TUBULAR SPLICING

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The purpose of studying repair of nerves in experimental animals, such as the rat, is to perform model experiments in which the phenomena inaccessible to large scale investigation in human subjects may be analyzed under controlled conditions. It is neither intended nor to be expected that the results obtained in such model experiments will become immediately applicable for clinical use. What is to be expected, however, is that the lessons learned from those experiments, when properly interpreted in terms of the conditions prevailing in the human body, may furnish directives for clinical research and possibly clinical practice. In a preceding article¹ a method of reuniting severed nerves by means of arterial cuffs was outlined, and the superior results of nerve regeneration following "sleeve splicing" were described. Since that publication, the method has proved its value on several hundred experimental animals, including rats, chickens, rabbits, cats and monkeys. We have gained from these studies much information about the prerequisites of nerve regeneration; above all, insight into the reasons for the success of the sleeve-splicing method. While it would be idle to predict whether or not the arterial sleeve will make a suitable link in human nerves, the lessons which we have learned from analyzing the mechanism of its action in animals are of such a general and fundamental nature that they may well be heeded in whatever method one may elect to follow in surgical practice. These lessons pertain particularly to the early stages of regeneration. As will be shown in this paper, the whole course of nerve regeneration is essentially decided within a matter of days or, at best, weeks after the nerve union. Most of the processes thereafter are determined by the conditions laid down during the initial phase of regeneration, and the prospects of eventual nerve restoration will benefit or suffer, depending on the success or the failure of the early union.

It is with these facts in mind that we present in this article an analysis of the events following sleeve splicing and an evaluation of their significance for successful nerve regeneration. Some of these phenomena are common to all kinds of nerve reunion, and others are peculiar to the sleeve-splicing technic. Some of the latter

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1. Weiss, P.: Nerve Regeneration in Rat Following Tubular Splicing of Severed Nerves, Arch. Surg. 46:525-547 (April) 1943.

are shared by other tubulation methods. In fact, Kirk and Lewis² in their excellent histologic study of nerve regeneration after fascial tubulization have noticed some of the phenomena emphasized by our studies. In the preceding study, the multiple functions of the arterial sleeve in facilitating nerve regeneration have been listed. These functions include insurance of straight and unbranched nerve fiber outgrowth, and prevention of escape of fibers, of invasion of connective tissue and of formation of fibrotic and growth-obstructing suture lines. The present study will furnish an account of how these functions are being exercised.

EXPERIMENTAL STUDY

MATERIAL AND METHOD

Our results are based on a study of 39 rat nerves, either tibial or peroneal, which were transected, reunited by means of an arterial sleeve and then studied between one and fifteen days after the operation. In general, the procedure described in the previous article¹ was followed. The arterial sleeves were so chosen as to fit comfortably over the nerve ends without producing constrictions. The ends of the nerves were not closely apposed but were left separated by a gap varying in extent from a fraction of to several times the diameter of the nerve, i. e., from about five-tenths to several millimeters. In some cases the gap became wider than was intended, owing to the partial retraction of one or both nerve stumps from the sleeve. In contrast to our earlier procedure, excess blood was not blotted from the interior of the gap but was left in place. This blood played an integral part in the healing process not formerly realized in its full meaning. As anesthesia induced with soluble pentobarbital U. S. P. was maintained for several hours, the seal between the nerve ends had become sufficiently firm by the time the animals resumed movement.

In order to investigate the phenomena taking place at the distal suture line of a graft in the absence of nerve fibers, splices between two peripheral nerve segments were effected. For this purpose, a piece several millimeters in length was excised from the proximal sciatic nerve. Two weeks was then allowed for the degeneration of the peripheral stump. After this period either the tibial or the peroneal nerve or both were transected and reunited by arterial sleeves. In this case neither stump contained intact nerve fibers, and such nerves will be referred to henceforth as "aneuritic." In 8 animals, simple biopsies of the union were made within two weeks after the operation, with special attention to the medium filling the sleeves between the nerve ends. The biopsy specimens from the remaining 31 nerves were straightened on cardboard, fixed in Bouin's solution, embedded in paraffin, sectioned serially at 10 microns and impregnated with silver according to Bodian, with an additional Mallory triple azan stain for the differentiation of connective tissue superimposed on the silver stain in sections selected at regular intervals. In all illustrations the proximodistal direction of the nerve is from bottom to top.

GENERAL RESULTS

Immediately after the operation, the artery is attached to the nerve ends by clotted blood and lymph. The gap between the nerve ends is filled with a dark purple blood clot visible through the translucent walls of the artery. This filling and the moderate tension along the nerve keep the arterial tubes from collapsing. Within four to five days after the operation the blood clot undergoes profound physical and chemical transformations. It is through these transformations that the severed texture of the nerve becomes rewoven in such a manner as to prepare the unimpeded transit of sheath cells and regenerating axons from one stump to the other. These changes are diagrammatically summarized in figure 1, representing the situation on the first, third and fifth days. Resolved into component steps, the reweaving process occurs as follows:

Phase 1.—Immediately after the operation, a firm connection between the nerve ends is established by the fibrin reticulum of the clotting blood in the gap, the fibrin threads inserting directly on the cut surfaces. The erythrocytes lie in clusters embedded in the fibrin meshes (fig. 1 *A*).

2. Kirk, E. G., and Lewis, D. D.: Regeneration in Peripheral Nerves, *Bull. Johns Hopkins Hosp.* 28:71-80, 1917.

Phase 2.—Within twenty-four hours most of the erythrocytes disintegrate, while the fibrin framework persists. Later proteolysis along the inner wall of the artery breaks the connections between the clot and the sleeve. Thus detached all around its circumference, while firmly cemented to the two nerve stumps, the cylindric clot becomes subjected to longitudinal tension.

Phase 3.—The fibrin net assumes preponderantly longitudinal orientation corresponding to the lines of tension (fig. 1 *B*).

Phase 4.—By the third day, fibrinolytic liquefaction has set in within the clot. Its action is differential in that it dissolves mostly the transverse threads of the fibrin meshes while sparing the longitudinal ones (fig. 1 *B*). Somehow tension has rendered the longitudinally oriented fibrin fibers more resistant to proteolytic destruction.

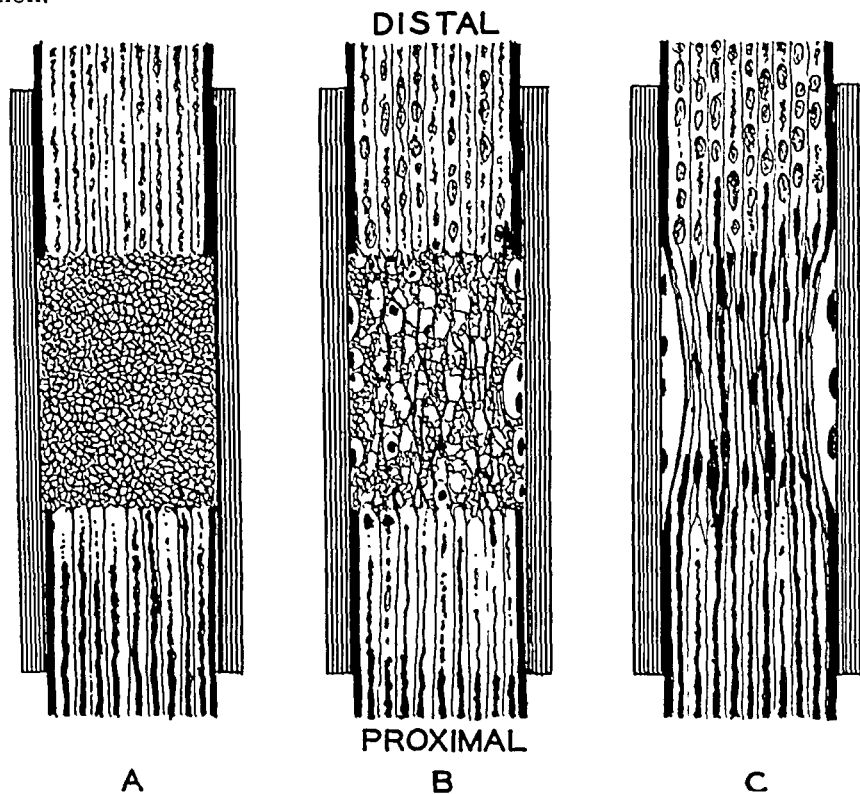


Fig. 1.—Diagram showing three stages in the transformation of the union tissue between sleeve-spliced nerve stumps, one (*A*), three (*B*) and five (*C*) days after the operation.

Phase 5.—By this time migration of cells into the region of the former gap has begun. Sheath cells and nerve fibers move out along the solid strands of fibrin and hence are likewise oriented in the longitudinal direction of the nerve. Simultaneously, macrophages move in and continue to clear the spaces between the fibers.

Phase 6.—By the fifth day, a continuous, straight cell bridge, followed by regenerating axons, extends across the former gap (fig. 1 *C*). The Schwann cells of this bridge stimulate the deposition of collagen along their surfaces, and a system of collagen fibers, oriented longitudinally, is laid down as the endoneurium of the nerve segment.

Phase 7.—When continuity between the nerve stumps is completely restored, channels are opened for the passage of endoneurial fluid, which may serve to keep the interior of the nerve in the required state of fluidity.

Comment.—This survey shows that the interweaving of severed nerve stumps occurs essentially by three successive processes: (1) the formation of an oriented scaffolding of fibrin fibers; (2) an oriented migration of living cells and nerve fibers, retracing and populating the fibrin matrix, and (3) a collagenization under the influence of these cells of the intercellular spaces in continuity with the stumps. By contrast, the scar forming between two nerve ends not protected by a sleeve fails to undergo longitudinal orientation, becomes invaded by all kinds of surrounding connective tissue cells and establishes a sort of foreign block in the continuity of the nerve. The two stumps, instead of being rewoven into an integral fabric over which sheath cells, nerve fibers, blood vessels and capillary liquid may pass freely and easily, are merely patched up by what amounts to a mechanical cementing tissue of low permeability.

These differences will become even more evident in the following day by day account of the healing progress. This account is based on the rate of progress as observed in the average case. While the timing varies slightly, depending on



Fig. 2.—Union by blood clot of sleeve-spliced nerve stumps, one day after the operation; *a*, wall of arterial sleeve ($\times 120$).

the age of the animal, the size of the nerves and the length of the gap, the fluctuations affect only the onset and duration, but not the order of succession, of the listed steps. For convenience, we shall designate the tissue filling the gap and reuniting the nerve stumps as the "union tissue," the term to be applied through all stages of transformation, beginning with the early blood clot and terminating with the restoration of the new nerve segment.

ONE DAY

Figure 2 shows the condition of the union after twenty-four hours. Degeneration of the axons in the peripheral stump has set in and some ovoids can be seen near the cut. Most axons are still intact, as it has been generally observed that wallerian degeneration within the sleeve is somewhat retarded, presumably owing to slight compression.³ One notices in the picture that the two stumps are cemented

3. Weiss, P., and Davis, H.: Pressure Block in Nerves Provided with Arterial Sleeves. *J. Neurophysiol.* 8:269-286, 1943.

by a blood clot firmly adherent to the cut surfaces. In contrast, there is a gap between the nerve and the arterial wall. This gap is an artefact resulting from the shrinkage of the preparation during fixation. However, the fact that this detachment has occurred along the arterial wall indicates that the clot does not adhere firmly to the artery, although its link with the two nerves is solid. The lack of firm ties between nerve and sleeve reduces, of course, the holding strength of the latter. On the other hand, we have regularly observed that the slipping out of the nerve ends from the sleeve is counteracted by the suction which such withdrawal would necessarily exert. With the sleeve gripping the surface of the nerve closely, the nerves act like the plungers in the barrel of a syringe; i. e., they could not be separated without creating a vacuum in between, and the suction of this vacuum helps to keep them in place as long as the pull remains moderate.

After the blood between the stumps has become clotted, it strengthens the formerly tenuous union between the nerve stumps. Blood in an otherwise empty artery, as one knows, would long remain liquid. In our arterial cuffs, tissue juice and exudates of the nerve ends obviously inhibit the antithrombic action of the artery. The

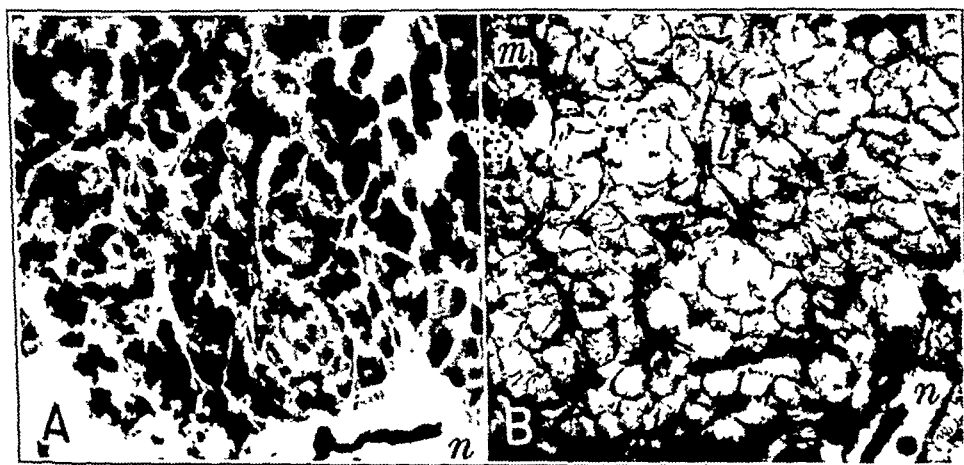


Fig. 3.—*A*, part of the union tissue of figure 2 under high magnification ($\times 630$); erythrocytes dark, fibrin framework light; *n*, cut end of an axon. *B*, union tissue early on the second day ($\times 630$); *n*, end of a cut nerve fiber; *m*, macrophage; *l*, leukocyte.

firmest attachment between artery and nerve is effected at the two ends of the artery where epineurial connective tissue grows over the sleeve, incorporating it in the continuity of the nerve. Under high magnification, the clot can be seen to be composed of small groups of erythrocytes, densely packed, lying in the meshes of a fibrin network (fig. 3*A*).

TWO DAYS

Biopsy on the second day already reveals the presence of a liquid menstruum inside of the sleeve composed, evidently, in part of serum oozing from the clot owing to syneresis, and in part of liquids released by the progressive destruction of the red cells and the liquefaction of fibrin. The fluid is still dark colored. More details can be seen in the histologic pictures. As in the one day preparations, the solid parts of the matrix are firmly cemented to the nerve ends but adhere only lightly to the wall of the artery. The red cells have mostly disintegrated, although their ghosts are still intact. Inspection under high magnification (fig. 3*B*) reveals the presence of a fine honeycomb of fibrin, the meshes of which are the spaces formerly occupied by the red blood corpuscles. The disappearance of the red cells

enables the white blood cells to stand out in the pictures. They consist of granular leukocytes, some lymphocytes and only an occasional macrophage. A sample count indicated about 3,000 of the larger leukocytes per cubic millimeter within the clot. There is a denser accumulation of these cells along the arterial wall, where many of them can be seen to liquefy the surrounding clot. Thus vacuoles appear in the clot all along its surface, each vacuole the product of a single cell. On becoming confluent, these vacuoles form a liquid layer, separating the clot from the artery. Figure 4 shows this process well advanced on the third day. Thus, while the clot from the beginning has failed to become sealed to the artery, it is now actively detached from it by this surface liquefaction.

This has a decided influence on the tensional pattern within the union tissue. The origin of these tensions is twofold. If the nerve ends tend to retract, they



Fig. 4.—Proteolytic detachment of the union tissue from the arterial wall; note confluent cavities around liquefying cells; *a*, sleeve wall; *s*, condensed surface of clot; *t*, liquefied space between *a* and *s* ($\times 240$).

put the intervening clot under elastic strain oriented longitudinally along the axis of the nerve. However, even in the absence of such extraneous pull, tensions arise within the clot owing to its syneresis. This syneresis, which is due to the progressive segregation of the solid from the liquid phases of the colloids of the clot, will contract the clot in those directions in which shrinkage is possible, i. e., where the surface of the clot is free. However, where it is attached internal tensions will arise between the points or surfaces of attachment. These elastic tensions will equal the force that would have to be exerted if the clot had first been allowed to shrink unimpeded and then been returned to the former length by actual stretching. Since the clot in all our cases is essentially a cylinder, attached at its base and top to the nerve stumps while free along its mantle, syneresis will lead to actual shrinkage

in the radial directions but to the setting up of elastic tensions in the longitudinal direction along which yielding is precluded by the resistance of the nerve ends.

In accordance with this tensional pattern, the fibrin framework, beginning with the second day, assumes a striking longitudinal organization (fig. 5 *A*), which, in view of the known orienting action of tension on the arrangement of fibrin fibrils, can be directly ascribed to the mechanical stresses in the clot. Concurrently with the increasing prominence of the longitudinal fibrin aggregates, a dissolution of the fibrin braces oriented otherwise than longitudinally takes place. Thus, the longitudinal parts of the fibrin network are strengthened while the nonlongitudinal ones are resorbed by proteolysis. Though this liquefaction is often more marked at first near the ends of the nerves, it likewise arises in many places in the interior of the clot more or less simultaneously. It results in a gradual increase in the size



Fig. 5.—*A*, transition from proximal stump to union tissue late on second day. Heavy fibrin fibers begin to appear in the longitudinal direction (lines of tension). Note scattered leukocytes and macrophages and liquefying activity of the latter (cavities) in the denser outer parts of the clot. *L-L*, level of transection, containing the ends of cut nerve fibers (*n*) ($\times 230$). *B*, union tissue on the third day. Note the destruction of the fibrin net, exempting the longitudinal strands ($\times 120$).

of the individual meshes, more and more of the meshes of the original honeycomb becoming confluent as the partitions are dissolved.

THREE DAYS

By the third day, the condition illustrated in figure 5 *B* is reached. Only the gap region, measuring several millimeters, is shown in the picture. One can see the lumen of the sleeve filled with a spongy mass consisting, according to its staining reaction, of fibrin. These are the ruins, as it were, of the original compact clot. Liquefaction along the wall of the sleeve has become very extensive, and so has the consequent detachment of the union tissue from the arterial wall. Large liquid spaces pervade the clot. The longitudinal fibrin strands have become even heavier

and straighter, and many extend throughout the clot. Viewed at higher magnification, the details of the transformation of the clot become evident (fig. 6 *A*). In some places, the outline of the original honeycomb of fibrin around red cell ghosts can still be seen, but most of the meshes have widened considerably, with marked elongation in the direction of the nerve. The heavier, longitudinal fibrin strands are clearly visible (compare also fig. 4), but they are still interconnected by cross links. As one can see from the picture, cells are still very scarce in the central portions of the union tissue. Near the nerve ends, however, cell migration has set in, as will be discussed presently. The longitudinal fibrin fibers are from their very first appearance anchored in the two cut surfaces of the nerve. This is already clear on the second day (fig. 5 *A*) but is even more marked on the third day. As the nerve fiber substance near the wound is at this stage liquid, the solid frame of the cut surface of the nerve consists of the rims of the neurilemmal tubes and



Fig. 6.—*A*, central portion of the union tissue on the third day, showing the advanced transformation of the fibrin network into longitudinal strands ($\times 630$). *B*, sheath cells (spindle-shaped) on the third day, climbing along the fibrin network; *a*, sleeve wall ($\times 630$).

the endoneural collagen. It is only along these solid lines that fibrin fibers can insert. Therefore, the fibrin framework forms in direct continuation of the architecture of the nerve stumps.

The degree of cell invasion observed at the end of the third day varies greatly among different cases. While in some the union tissue may not contain more than a few isolated Schwann cells, in others some strands of such cells may have moved clear across and reached the opposite stump. In practically all cases, however, the invasion from the cut surfaces has started on a broad front. The outgrowing sheath cells (fig. 6 *B*) move definitely as single, slender, spindle-shaped cells with far drawn out ends,² staining heavily with silver.⁴ Several sheath cells may follow

4. Holmes, W., and Young, J. Z.: Nerve Regeneration After Immediate and Delayed Suture, *J. Anat.* 77:63-96, 1942.

each other in tandem arrangement, but they do not, at this stage, offer the appearance of those smoothly contoured Schwann bands seen during later phases. The sheath cells can be seen to move without exception along the heavy fibrin fibers of the union tissue. While there are still some transverse fibrin connections, sheath cells may follow them to cross from one strand to another, as seen in figure 6*B*. However, such deviations are temporary and cease with the gradual breakdown of the fibrin cross links. Sheath cell migration proceeds from both nerve stumps. The presence of a noncellular "no man's land" between the stumps in our cases has permitted us to establish this point with certainty.

Along with the sheath cells, macrophages appear in the region near the wound. Since these macrophages have not previously been present in the interior of the clot in such numbers, it is evident that most of them have come from the nerve. They may be mobilized cells of the endoneurial tissue. Theoretically, there is a possibility that some of them may be transformed sheath cells. One of us (P. W.) has recently observed the transformation of sheath cells into cells of the macrophage type in tissue cultures of embryonic chick ganglions. However, whether this can also occur in the body remains to be demonstrated, and nothing we have thus far seen suggests this possibility. Macrophages seen after nerve section are usually described as engaged in a one way traffic into the nerve fibers. Yet our present observations prove that numbers of them move in the opposite direction, i. e., from the nerve into the union tissue. Their relatively late appearance on the scene disqualifies them as the primary agents of proteolysis. Liquefaction is well under way before they arrive in larger numbers. On the other hand, once present, they participate in the proteolytic activity and dissolve the remaining fibrin threads in their way. Again, as in the preceding phase, the longitudinally oriented fibrin fibers resist this dissolution.

FOUR DAYS

The fourth day brings merely an elaboration of the phenomena observed on the third day, with both the straightening of the union tissue and the immigration of cells into it progressing rapidly. Moreover, formation of new blood vessels and the outgrowth of regenerating axons are becoming more conspicuous. Well formed blood vessels can be seen to traverse the scar as early as on the third day, but more frequently on the fourth day. Significantly, these vessels arise as direct continuations of the vessels of the proximal and distal stumps and course in the longitudinal direction without much branching. This contrasts with the vascularization of an ordinary suture scar, into which the blood vessels penetrate from the epineurial and extraneural spaces (fig. 11*A*). Apparently the regenerating blood vessels, like the other components of the regenerating nerve, are guided by the fibrin architecture of the union tissue. A well oriented union tissue thus insures straight vascular reconnection between proximal and peripheral stumps.

Most of the axons of the peripheral stump have, in the meantime, disintegrated. In the proximal stump, the initial retrograde changes near the wound have been superseded by axon regeneration. Many of the new sprouts have arrived at the old level of the cross section and have proceeded into the union tissue. In doing so, they follow the same longitudinal guide lines as the sheath cells. The relative simplicity and clarity of the conditions in the clot make these cases favorable objects for the study of the relation between regenerating sprouts and sheath cells. As a general result of many observations on such preparations, we have become convinced that the vast majority of newly sprouting axons is closely associated with sheath cells. Contact need not exist over the full length of the axon, at least not during the earlier

phases. Some stretches may be bare, much as they are in early development.⁵ This fact makes it difficult to decide whether there are any sprouts that travel in complete independence of sheath cells. That they can do so for a certain distance is evident in our preparations. It is equally clear, however, that such bareness is the exception rather than the rule.⁶

Some branching of the outgrowing sprouts does occur at nodal points of the fibrin network. However, such branching remains on a minor scale. Also most of the side branches are abortive, particularly those that do not run longitudinally. Presumably as the cross links among the longitudinal fibrin threads are progressively resorbed, nerve fibers which happen to have started to grow out along them are being deprived of their support and are then likewise reduced. This process soon leaves only those nerve fibers in the field which have grown out straight and essentially unbranched.



Fig. 7.—*A*, restored union between proximal and distal stump on the fifth day; *a*, sleeve wall; *h*, fresh hemorrhage ($\times 120$). *B*, strands of sheath cells, axons and macrophages in the union tissue of the same case as shown in figure 7 *A* ($\times 630$).

FIVE DAYS

By the fifth day, the orderliness of the reconnection between the proximal and the distal stumps has become fully apparent. By now, most of the union tissue has been pervaded by sheath cells and regenerating nerve sprouts, and the former clot has become fully converted into a new integral segment of nerve. As one can see from figure 7 *A*, the new nerve segment has cleanly retracted from the arterial wall, the space in between being taken up by a liquid residue of the pre-

5. Speidel, C. C.: (a) Studies of Living Nerves: I. The Movements of Individual Sheath Cells and Nerve Sprouts Correlated with the Process of Myelin-Sheath Formation in Amphibian Larvae, *J. Exper. Zool.* **61**:279-331, 1932; (b) II. Activities of Ameboid Growth Cones, Sheath Cells, and Myelin Segments, as Revealed by Prolonged Observation of Individual Nerve Fibers in Frog Tadpoles, *Am. J. Anat.* **52**:1-79, 1933.

6. Nageotte, J.: *L'organisation de la matière dans ses rapports avec la vie*, Paris, Félix Alcan, 1922. Kirk and Lewis.² Holmes and Young.⁴

ceding liquefaction. The streams of sheath cells, which have emigrated from the two nerve stumps, have met and merged into a continuous cell bridge. Restoration of their continuity obviously terminates their further migration and proliferation, for these sheath cell streams never show any tendency to continue to grow into local gliomas. Macrophages are now present in large numbers and by their liquefying power keep the channels between the outgrowing cell strands clear (fig. 7B). Some scraps of the old fibrin network are still present in spots but are apparently being removed by the macrophages. At the same time, collagen begins to appear along the surface of the sheath cells, and the formation of neurilemmal sheaths and true endoneural connective tissue is thus initiated. Axons have continued to grow along the longitudinal pathways without further attempts at branching, and many of the most advanced sprouts have already penetrated into the distal stump, even in cases in which the original gap between the nerve ends measured as much as 5 mm. The original network of the clot has by now become completely resolved into a system of independent longitudinal strands.

SEVEN DAYS

By the end of the first week, the healing process is essentially accomplished. At this time, the former scar region can no longer be distinguished as such, and most traces of the former cut surfaces have become abolished, with the exception of the old margin of the perineurium, which has remained sharply outlined.¹ The nerve fibers extend now in strictly oriented straight and parallel strands from the proximal into the peripheral stump (fig. 8). They are still separated by larger liquid spaces than would be found in the normal nerve. These spaces, however, do not represent edema of the kind described in an earlier paper⁷ but are residues of the local liquefaction which has been maintained throughout the healing process. Just when movement of endoneurial fluid along these spaces will be resumed, enabling such fluid to pass freely from the proximal to the distal stump, cannot be determined without special experiments. It is probable, however, that the endoneurial humors take over where the local liquefying activities of the healing process leave off in providing for fluidity of the nerve spaces.

LATER STAGES

A comparison of a splice after two weeks with that after one week reveals no new developments except an increase in the number of regenerated fibers. The new fibers tend to grow out along the surfaces of the more advanced ones, and thus small bundles are built up by a principle which has been described in an earlier paper⁸ as "fasciculation." From then on, further improvement in the condition of the newly formed region will consist essentially of increase in the diameter of the nerve fibers, deposition of myelin and collagenization of the endoneurial tissue. Secondary resorption of excess collaterals, assumed to follow excessive branching and abortive sprouting in ordinary suture lines, is not encountered in our preparations, as branching has remained negligible.

As for the nerve sheath, the arterial sleeve may permanently serve as perineurium.¹ In many cases, however, enough epineurial tissue had been tucked into the sleeve during the operation to introduce a small source of epineurial proliferation into the lumen. However, since its growth is forced into the same longitudinal orientation that characterizes the rest of the union tissue, it merely forms a thin

7. Weiss, P.: Endoneurial Edema in Constricted Nerve, *Anat. Rec.* **86**:491-522, 1943.

8. Weiss, P.: Nerve Patterns: The Mechanics of Nerve Growth, *Growth* **5**:163-203, 1941.

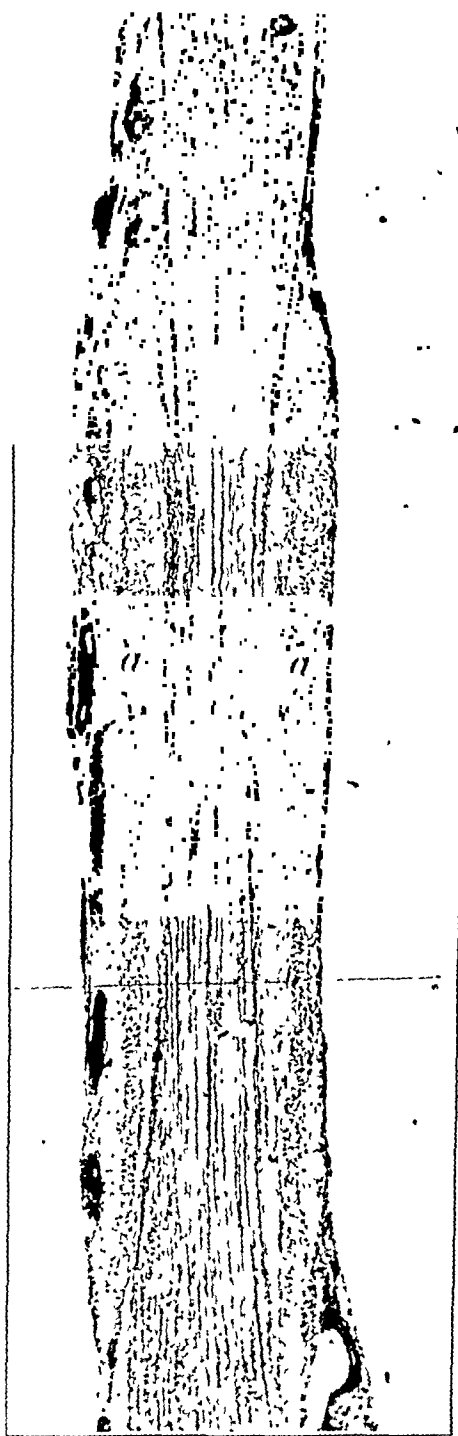


Fig. 8.—Completed union on the eighth day, a, sleeve ($\times 48$).

cylindric layer separating the nerve proper from the inner arterial wall. In no case have we seen an infiltration of this tissue into the interior of the nerve.

THE UNION OF ANEURITIC NERVE STUMPS

In the case of nerve grafts, the connection between the proximal nerve stump, as source of innervation, and the graft is effected in the manner described in the preceding pages. The union of the peripheral end of a graft with the distal nerve stump, however, is somewhat different, in that it involves the union of degenerated "aneuritic" nerve fibers, none of which contain axons. Since difficulties encountered by nerve fibers when they later reach the distal end of the graft have often been blamed for the lack of success of grafting in general,⁹ we made a special investigation of the healing process at the "distal suture line." As was to be expected, the events there were in all essential points identical with those observed at the proximal suture line; i. e., the arterial sleeve had the same organizing effect on the union tissue and, in further consequence, on the reconnection of the two severed ends. There were some minor differences, however, attributable to the different constitution and consistency of the aneuritic fibers in this region.

As was outlined on page 420, the nerves of this series were allowed two weeks of predegeneration prior to the splicing operation. They were therefore in a different condition from nerves in primary suture. The nerve fibers had become converted into true Buengner cords; axons and myelin had disappeared, and sheath cell hypertrophy and hyperplasia had already led to the formation of relatively solid bands of protoplasm inside the neurilemmal tubes, in accordance with the classic descriptions by Ramon y Cajal, Boeke, Nageotte and others. In brief, the irritative and regressive changes following primary nerve section had subsided, and the cells were already in proliferation. Consequently, it was not surprising to find that the reconnection between such aneuritic nerve stumps after sleeve splicing occurred even more promptly than that between stumps after primary transection. While the general organization of the union tissue two days after the operation is much the same as previously described for that stage, sheath cell migration is already as extensive as it would ordinarily be about the fifth day. This difference is readily explained by the fact that after primary nerve section the sheath cells are not immediately in a condition to migrate and will not acquire this faculty until after the breakdown of the neurite, while in the predegenerated nerve they had already passed through this preparatory phase.¹⁰

Sheath cell growth occurs again along a foundation of oriented fibrin, which arises in the same manner as in primary sutures. Figure 9 shows the borderline between one nerve stump and the union tissue on the third day after splicing. It clearly illustrates how the fibrin network is connected with the old collagen system of the nerve. This favorable picture has been obtained because sheath cell emigration in this case had, for some unknown cause, been delayed. One recognizes the anchoring of the fibrin network all along the old surface of the nerve, the longitudinal fiber strands becoming heavy and straightened, while the transverse connections are being dissolved. A moderate number of leukocytes and a few macrophages can also be seen. The membrane-like border between the old nerve

9. Davis, L., and Cleveland, D. A.: Experimental Studies in Nerve Transplants, *Ann. Surg.* **99**:271, 1934.

10. Ingebrigtsen, R.: A Contribution to the Biology of Peripheral Nerves in Transplantation: II. Life of Peripheral Nerves of Mammals in Plasma, *J. Exper. Med.* **23**:251-264, 1916. Abercrombie, M., and Johnson, M. L.: The Outwandering of Cells in Tissue Cultures of Nerves Undergoing Wallerian Degeneration, *J. Exper. Biol.* **19**:266-283, 1942.

fibers and the fibrin lattice consists of collagen. It can be attributed to the fact that the cross section of aneuritic nerves contains a solid mass of cells and intercellular matrix, while the cross section of freshly transected nerves is riddled with the lumens of nerve fibers in initial degeneration. It is unlikely that this fine collagenous lamella could present a permanent barrier to nerve regeneration, since macrophages coming up against it from the old nerve tubes seem to puncture it promptly.

At the end of seven days, the continuity between the spliced nerve stumps is fully restored by cellular strands in straight parallel alinement. As seen in figure 10 *A*, the nerve again assumes the center of the sleeve lumen, while the space between nerve and wall is filled with residual liquid from the liquefaction of the



Fig. 9.—Transition from an aneuritic nerve stump (below) to the union tissue (above) on the third day ($\times 240$).

clot. Blood vessels again pass straight from one stump to the other (fig. 10 *B*), following the general orientation of the union tissue. Figure 10 *B* gives a detailed view at higher magnification of the union tissue of the nerve shown in figure 10 *A*. One recognizes the long slender parallel cylindric bands of sheath cells, and a longitudinal blood vessel (*b*).

Preparations of this kind are particularly favorable for the study of the problem of collagen formation in nerves. This problem has aroused some interest in connection with the peripheral nerve tumors. Without entering into the neuropathologic aspect, we can state that our preparations make it absolutely clear that collagen is formed along the surface of the sheath cell. The longitudinal bands of sheath cells, being enclosed in a tubular neurilemmal sheath, are so characteristic in appearance that it would be impossible to confound them with the scattered elements of

the endoneurial connective tissue. In their outgrowth, the Schwann cell cords retain their characteristic tandem arrangement. While in an ordinary nerve scar these strands are intermingled with cellular elements of the scar region, the condition of the arterial splice lets them push forth into a cell-free medium, almost like tissue culture. We see these bands then glide along the fibrin strands into the former gap, often unaccompanied and undisturbed by any other types of cell. They represent, in a sense, pure cultures of sheath cells, and it is along their surface that the Mallory triple azan stain reveals the first identifiable deposit of collagen in distinct blue. Only later, finer collagen fibers appear in the spaces between individual cell bands, and even this may occur some time before endoneurial fibroblasts



Fig. 10.—*A*, completed union between two aneuritic stumps on the seventh day. *L*, levels of the old cut surfaces ($\times 76$). *B*, detail of the union illustrated in figure 10 *A*; *b*, blood vessel ($\times 630$).

have moved in. No similar collagen formations were ever observed around other sorts of cells in the early union tissue. These observations, therefore, fully confirm the view of Nageotte¹¹ and Masson¹² that collagen, and particularly the collagenous sheath of the individual nerve fiber, is a joint product of the sheath cell and its surrounding matrix, with the surface of the sheath cell as the seat of the primary action. The question of collagen formation in nerve is of considerable importance in connection with the practical problem of nerve fibrosis. It seems that serious

11. Nageotte, J.: Substance collagène et névroglie dans la cicatrisation des nerfs, *Compt. rend. Soc. de biol.* **79**:322-327, 1916.

12. Masson, P.: Experimental and Spontaneous Schwannomas (Peripheral Gliomas), *Am. J. Path.* **8**:367-416, 1932. Murray, M. R., and Stout, A. P.: Schwann Cell Versus Fibroblast as the Origin of the Specific Nerve Sheath Tumor, *ibid.* **16**:41-60, 1940.

attention should be given to the sheath cells in this respect, for they represent a potential intrinsic source of fibrosis.

NERVE REUNION WITHOUT SPLICING

As a background with which to contrast the effects of arterial splicing, we have made a number of control experiments in which a nerve was merely transected and the two ends then left in close apposition without further intervention. If the apposition was good, mechanical reunion between the ends took place within a surprisingly short time. After five days, the two ends were found to be firmly cemented by intervening scar tissue (fig. 11 *A*). However, the constitution of the union tissue was fundamentally different from that observed in sleeve-spliced nerves. The main points of distinction are the following: The liquefaction within the clot has failed to occur. Instead, dense fibrous connective tissue from the surfaces

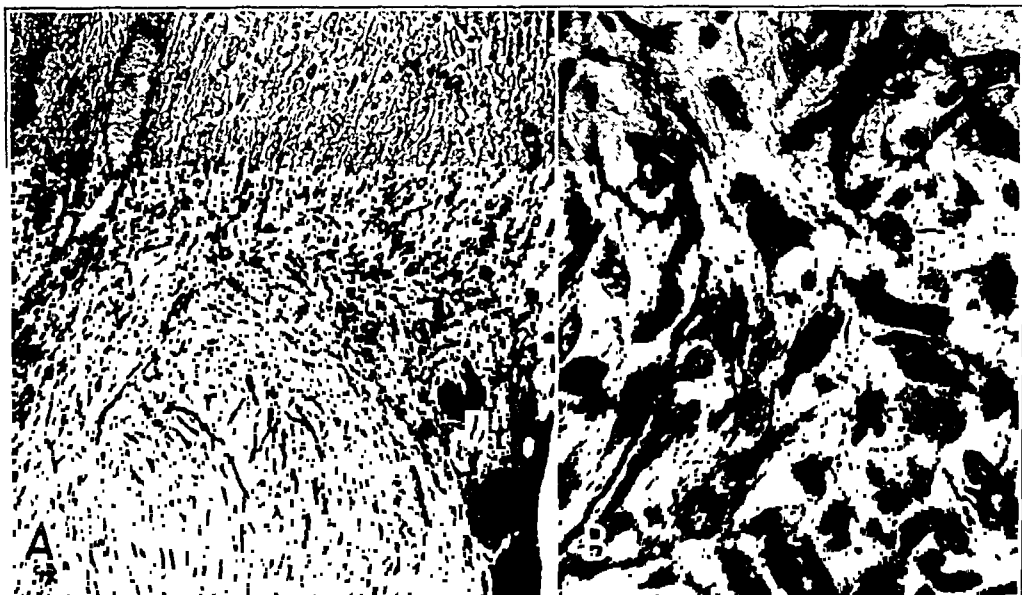


Fig. 11.—*A*, union between unsplined tibial nerve stumps on the fifth day. Note condensation and disorientation of scar tissue; *b*, epineurial blood vessels penetrating into the scar. The confused scar of this figure is to be compared with the well oriented union shown in figure 7 *A*, illustrating the sleeve-spliced peroneal nerve of the same animal; both nerves had been transected at the same level ($\times 63$). *B*, enlarged view of the scar of figure 11 *A* ($\times 550$). This figure is to be contrasted with figure 7 *B*, taken from the sleeve-spliced fellow nerve of the same animal.

of the nerve has penetrated into the region between the stumps and has given rise to a chaotic tangle of cells and fibers. Heavy lymphocytic infiltration accompanies the radial ingrowth of blood vessels from the vicinity. Adhesions between this scar tissue and its surroundings, resulting from the extraneural origin of these cells, cause the establishment of a tensional pattern which, in the main, converges radially toward the lesion. This is not conducive to the establishment of straight connections between the severed stumps. The outgrowing sheath cells and nerve fibers take correspondingly confused courses (fig. 11 *B*). As has been described by earlier observers, the regenerating axons branch profusely in the scar, with branches of the same fiber becoming distributed over widely separated regions of the scar and, hence, the distal nerve stump.

In short, unattended nerve stumps, even with cut surfaces closely approximated, fail to provide the conditions which we have recognized as indispensable for optimal nerve regeneration and which are actually obtainable by arterial splicing. The main shortcoming lies in the lack of lateral isolation of the union tissue. Indiscriminately adhering to the surrounding tissues as well as to the nerve ends, the initial clot develops a tensional pattern radiating in all directions and, consequently, preparing inroads from all sides for fibrous connective tissue. Moreover, as there are no provisions to prevent the dissipation of the proteolyzing factors from the union tissue, the latter cannot maintain that looseness of texture which ostensibly is a prerequisite of adequate nerve regeneration. As a result, instead of weaving an integral link between the nerve stumps, the union tissue becomes a foreign block in the continuity of the nerve. The fact that even so, owing to the luxuriant axon branching in such scars, numerous nerve fibers finally get through does not reduce the contrast between such unaided unions and the straight reunion of sleeve-spliced stumps. If we add that stitching the nerve ends with foreign suture threads, particularly in small nerves, only aggravates the disorganization of the tensional pattern at the suture line, the potential merits of sleeve splicing become apparent.

COMMENT

The observations reported in the preceding pages add up to a consistent and coherent picture of the healing process by which nerve stumps in an arterial sleeve are reunited. They likewise reveal the essential mechanisms involved. While individual cases show a certain variability of timing, the sequence of events is the same in all cases. These events duplicate essentially the course of action by which tension affects tissue growth in general and which was originally demonstrated and analyzed in tissue culture.¹³ According to those earlier experiments, the mechanism operates in two phases: First, tension forces the colloidal matrix of the tissue to assume orientation along the lines of stress, which in turn gives rise to fibrillar arrangements of corresponding orientation; second, cells of the spindle cell type, when growing into the matrix, advance and proliferate along the oriented fibrillar framework of the matrix; as a result, the orientation of the cells coincides with that of the original tensions.¹⁴ The same mechanism was later shown to underlie the oriented growth of nerve fibers as well.¹⁵ At the same time, further evidence was obtained to show the active participation of the colloidal matrix in creating those tensions to which it owes its eventual organization. A matrix consisting of a fibrin clot, for instance, tends to shrink owing to the progressive segregation of the solid and the liquid phases (syneresis, coacervation). This sets up contractile forces in the solid parts. Tensions thus generated within the clot combine with those imposed from the outside. All this has been known from the tissue culture experiments. But we readily recognize now that exactly the same mechanism operates in the reunion of sleeve-spliced nerve stumps. It is supplemented, however, by some additional features which had not been previously recognized, as, for instance, the differential liquefaction of the clot. The primary role of the artery is to give this tensional mechanism free play. How it performs this role is briefly discussed in the following paragraphs.

13. Weiss, P.: Erzwingung elementarer Strukturverschiedenheiten am in vitro wachsenden Gewebe: Die Wirkung mechanischer Spannung auf Richtung und Intensität des Gewebewachstums und ihre Analyse, *Arch. f. Entwicklungsmechn. d. Organ.* 116:438-554, 1929.

14. Weiss, P.: Functional Adaptation and the Role of Ground Substances in Development, *Am. Naturalist* 67:322-340, 1933.

15. Weiss, P.: In Vitro Experiments on the Factors Determining the Course of the Outgrowing Nerve Fiber, *J. Exper. Zool.* 68:393-448, 1934.

GAP FILLING

Nerve section invariably produces a gap between the stumps. Even what macroscopically appears as closest apposition still is a gap when viewed from the microscopic dimensions in which the cells that are to repair the defect operate. Gaps in tissue can be closed and repaired only by migration and growth of cells. This migration and growth can proceed only if certain physical and chemical requirements are satisfied, and foremost among these requirements is the presence of a proper physical substratum along which the cells may grow. Neither tissue cells nor nerve fibers can push forth into a homogeneous space, either gaseous or liquid; they extend only along phase boundaries (interfaces). The adequacy of a growth medium for cells and nerve fibers is, therefore, in part determined by its capacity to provide interfaces of the proper constitution, orientation, dimensions and numbers. The medium present between two severed nerve stumps is therefore of prime importance in that it must lay the foundation for the subsequent growth of a cell bridge.

Our experiments indicate that whole blood serves this function adequately. The *fibrin of the blood clot furnishes the fabric subsequently to be molded by tensions* into a system of tracks for cell and nerve fiber growth while the spacious meshes temporarily occupied by erythrocytes constitute spare room to be taken up by the invading cells. One must never lose sight of the fact that cells, like any physical bodies, can move into a circumscribed area only if they can displace a corresponding volume of substance. Liquids are easy to displace. However, if the clot consisted predominantly of compact matter, such as, for instance, fibrin, the cells would have much harder going and could penetrate only in limited numbers. It is for this reason that any filling above a certain density, even though having good cementing power and proper orientation, will be detrimental to nerve regeneration. This seems to be particularly true of pure or fortified blood plasma. Lacking the red cells, which after disintegration will contribute to the liquid phase, such a clot contains an unduly high ratio of solid fibrin to liquid constituents and therefore presents a handicap to growth. We have made a number of comparative studies, using blood plasma as filling in sleeves, and have found this medium almost invariably too dense for good nerve growth. It produces fibrotic islands leading to small local neuromas of arrested and choked nerve fibers. While the blocking effects of pure blood plasma may be negligible in the case of close apposition of the nerve ends, e. g., after "plasma suture,"¹⁶ they would become definitely objectionable in the presence of a gap of even a few millimeters. We are still investigating the optimal composition of the gap filling, and if a matrix superior to whole blood should be found, the results will be reported at a later date.

Our observations have brought no confirmation of the earlier contention¹⁷ that endoneurial fluid may be an important factor in determining the properties of the union tissue during the early stages of healing. While such fluid is probably instrumental in keeping the nerve channels clear after the first healing period is over, it seems to play no part in the establishment of the channels. Some contribution of the nerve ends to the gap filling is essential, however, in form of clotting factors. Whole blood enclosed in an arterial sleeve would remain liquid, owing to the anticoagulant properties of the wall of the sleeve. However, with nerve ends inserted, it clots.

16. Young, J. Z., and Medawar, P. B.: Fibrin Suture of Peripheral Nerves, *Lancet* 2: 126-128, 1940. Tarlov, I. M., and Benjamin, B.: Autologous Plasma Clot Suture of Nerves *Science* 95:258, 1942.

17. Weiss (footnotes 1 and 7)

TENSIONAL ORGANIZATION OF THE UNION TISSUE

The events of the second and third days are essentially concerned with transforming the original blood clot into a system of longitudinally oriented pathways for subsequent cell and fiber growth. This could be ascribed to some unknown "orienting factors" emanating from the two nerve ends, but both past experience and the evidence of the present experiments identify the operating factor as tension. These tensions arise partly outside, partly inside of the clot. Extraneous tension is due to whatever pull the nerve ends exert. There is a definite tendency of freshly cut nerves to retract beyond the initial distance during the days following transection. This gradual retraction works in the right direction, in that it places the union tissue under longitudinal strain. It is here that the elastic properties of the sleeve come into play. If the nerve ends are rigidly connected by sutures spanning the gap, all tensile stresses in the direction of the nerve will be taken up by the rigid suture threads, and the parts lying in between will sustain no stretch whatsoever. Only an elastic or plastic link permits the transmission of tensions to the substance filling the gap, where they may then exert their molding effects. As mentioned before, another effective source of tensions lies, however, in the shrinkage of the clot itself, and this type can of course operate even within rigid tubes or between nerve ends otherwise rigidly united, provided that the right amount of contractile material is present between the ends.

The configuration of the tensional pattern depends on how and where the clot is attached to its surroundings. No elastic tensions can develop in directions in which the material is free to contract. The points of attachment, therefore, determine the resultant stresses. An ideal pattern of longitudinally oriented stresses will arise in a clot attached at both ends to the nerve stumps but unattached over the rest of its circumference. The arterial sleeve is instrumental in bringing about this optimal tension pattern (fig. 12 *A*). It does so by preventing the clot from adhering along its sides. From its very beginning, the clot fails to bind intimately with the arterial wall. During the second and third days, this lack of adhesion is then further accentuated by active detachment from the sleeve. This is effected by migrating cells of the leukocyte type which spread rapidly along the wall of the artery and liquefy the adjoining surface layer of the clot (fig. 4). How many of these cells have emerged from the interior of the clot and how many have come from the nerve stumps, it has not been possible to determine. Some of them may be remnants of the arterial endothelium. However, most of the original lining is presumably scraped off during the splicing operation. Moreover, the lateral detachment has also been observed in sleeves made from frozen-dried arteries, in which the original endothelium had certainly perished. Whatever their origin, these cells produce a liquid layer which effectively separates the clot from contact with the sleeve. They might achieve this either by secreting a fluid or by secreting proteolytic enzymes which will digest the fibrin and thus liberate serum previously entrapped in the meshes of the coagulum. The presence of distinct erosion cavities around each cell (fig. 4) suggests proteolytic action.

Any residual local attachment between clot and arterial wall introduces distortion of the longitudinal tension pattern and entails a corresponding diversion of cell and fiber growth. The extreme of this condition is observed when severed nerve ends are left unsheathed (fig. 11 *A*). In these circumstances the clot is attached along its entire surface, which, moreover, owing to its continuity with the tissue spaces, is extremely irregular. Consequently, the pattern of tensions resulting from the gradual contraction of the clot is likewise irregular. Granting that blood seeps more readily into the extraneural spaces than into the rather tightly packed

nerve, it is obvious that the predominant orientation of the resulting fibrin framework will be in the direction of the tissue spaces, i. e., transversal with regard to the nerve. Radiating fibrous adhesions with ample pathways for the ingrowth of fibrous tissue and capillaries into the gap and outgrowth of nerve fibers and sheath cells from the gap would be the result. These hazards can be avoided only by preventing the clot from forming lasting lateral adhesions. It is in their effect on this early phase of the healing process that the various methods recommended in the past for wrapping or tubulating the suture line will have to be assessed. Their varying effectiveness in this regard may explain the great variability of results obtained by different authors. The arterial sleeve still appears to be the most natural preventive.

It is understandable now why even small breaks or pores in the arterial wall cause disturbances of nerve regeneration out of proportion to their actual size.

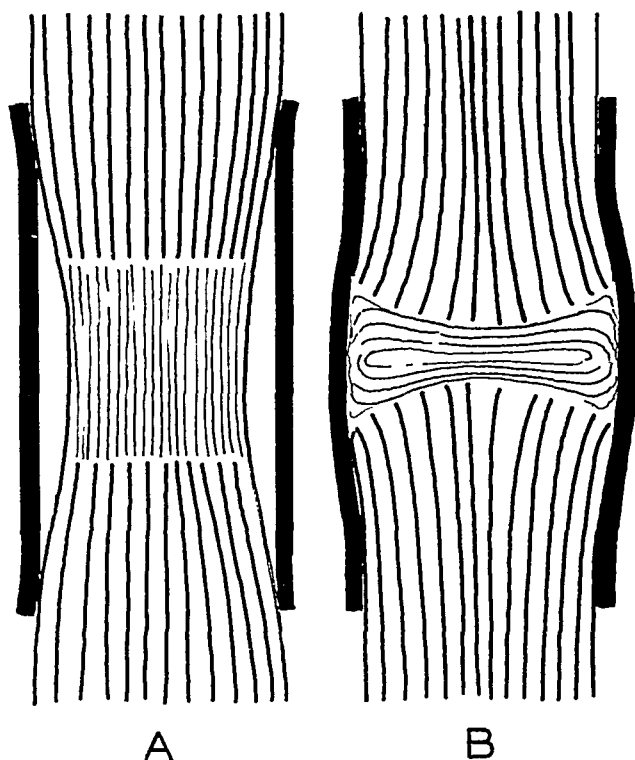


Fig. 12.—Diagram to illustrate the lines of stress in clots subjected to tension (A) or pressure (B) in the direction of the nerve.

They become centers of adhesion which deflect the whole tensional pattern in their direction (see fig. 5 of the earlier paper¹ on the subject). Similar difficulties have thus far militated against the use of heteroplastic arteries, both fresh and preserved. Large parts of the wall of a heteroplastic sleeve succumb to heavy lymphocytic attack in the foreign host body, and each focus of destruction becomes a potential source of adhesion and minor neuroma. If the host reaction could be delayed until there has been time enough for a well oriented union tissue to form, the sleeve would have served its main function, and the use of heteroplastic arteries might yet become feasible. On the other hand, there is no reason why other elastic tubes of nonirritant materials could not be substituted for artery, provided they

share the faculty of inducing fibrinolysis along their walls. Tubes fashioned from actively secreting epithelium or endothelium should serve this function adequately. We have found frozen-dried and rehydrated arteries fairly satisfactory, although occasional adhesions between union tissue and wall have been observed.

Aside from lateral adhesions, a major source of deflection of the tensional pattern is pressure of the two nerve ends against each other. Attempts at producing "close apposition" will have this effect. The nerve ends will become flanged and any blood clot forming in between, if it has no lateral outlet, will become subjected to compression in the direction of the nerve. The resulting tension pattern is shown in figure 12 *B*, and an actual example in a three day old splice is presented in figure 13. As subsequent growth of sheath cells and nerve fibers would retrace the fibrin pattern, the detrimental effects of this kind of union on nerve regeneration can easily be predicted from the pictures. By analogy we may assume that the presence between the nerve ends of air bubbles or liquid with excessive turgor will have similar effects.



Fig. 13.—Transversally oriented union tissue between improperly set aneuritic stumps on the third day ($\times 120$).

Once the correct tensional pattern has been established, the further course of events takes place almost automatically. The stress pattern first produces a corresponding orientation of the fibrin. The fact that oriented tension causes fibrin orientation in blood plasma clots has been a matter of record.¹⁸ It is evident from our preparations that the fibrin fibers not only assume preferential lengthwise orientation but become heavier when oriented along the lines of stress. This increase may be ascribed to the greater ease with which smaller fibrillar units can aggregate into larger bundles when they are parallel. Eventually the lines of stress become thus embodied in a system of material lines of fibrin destined to form pathways for cells and fibers. This constructive process is soon joined by a destructive process in which the formation of oriented structures is further accentuated by the simultaneous destruction of unoriented ones.

18. Baitsell, G. A.: A Study of the Clotting of the Plasma of Frog's Blood and the Transformation of the Clot into a Fibrous Tissue, *Am. J. Physiol.* **44**:109-131, 1917. Nageotte.⁶ Weiss.¹⁷

LIQUEFACTION

The dissolution of the interior of the clot begins about the second day (fig. 5 *A*) and from then on proceeds fairly rapidly. Biopsies after the second day usually show the sleeve filled with a pinkish fluid of low viscosity. This liquid menstuum is still rich in coagulable colloids, which when treated with the ordinary histologic fixatives produce a fine granulation. They give a strong Millon reaction for protein. Inasmuch as this liquefaction spares the heavier fibrin threads, which are oriented longitudinally, it does not lead to complete destruction of the clot but merely loosens its texture. In establishing longitudinal liquid channels, it prepares the ground for the later invasion by cells and fibers and, at the same time, counteracts any tendencies of the clot to become too compact and dense. In view of this fact, this phase of proteolysis seems almost an indispensable prerequisite for good nerve regeneration. The source of the liquefying agents becomes, therefore, a problem of considerable interest. While the problem has as yet been given only casual attention, the following facts have been gathered from our various observations.

Erythrocytes begin to disintegrate soon after the operation, and most of them have been destroyed by the second day. It is doubtful, however, that they release in their breakdown fibrinolytic enzymes, since it is unlikely that such enzymatic action would have remained undiscovered. A more familiar source of proteolysis is present in the blood clot in the form of granular leukocytes.¹⁹ Studies on inflammation, as well as tissue culture observations, indicate that such white cells begin to disintegrate after about twenty-four hours, and, inasmuch as they are known to contain proteolytic enzymes, the liberation of such agents en masse at the end of the first day would readily explain the observed onset of liquefaction just about that time. A third possibility, namely, the exudation from the nerve itself of fluid rich in proteolytic enzymes,⁷ cannot be wholly excluded, but our preparations reveal no fact that would encourage this view. If it were correct, liquefaction of the clot should proceed from the nerve ends toward the middle; yet no such systematic progress has been observed. On the contrary, centers of liquefaction are usually scattered more or less evenly throughout the clot (figs. 5 *B*, 6 *A* and 9). The fibrinolysis of the clot has no relation to blood vessels. It may appear prior to the ingrowth of blood vessels, or, in the case of early revascularization, it occurs wholly independently of the locations of the young vessels.

Proteolysis attacks first the fine tracery of fibrin outlining the spaces formerly occupied by the erythrocytes. Thus the meshes of the fibrin reticulum become larger and larger. It is only then that macrophages appear on the scene in larger numbers. A few scattered macrophages have been observed from the very first stages (figs. 5 *A* and 9). Wherever present, they liquefy the immediate surroundings. However, they are too scarce at first to be considered as the main agents of the primary liquefaction. After the third day, however, they become much more abundant, particularly in those parts of the clot adjoining the cut surfaces of the nerve (fig. 7 *B*), and from then on they seem to take a definite part in further fibrinolysis. Their accumulation around the nerve ends leaves no doubt that they have emigrated from the nerve stumps, for there is no other source that could have provided them. As they push toward the middle of the clot from both ends, they dissolve whatever fine interconnections between the longitudinal fibrin strands have survived the preceding stage of liquefaction. The

19. MacCallum, W. G.: *A Text-Book of Pathology*, ed. 6, Philadelphia, W. B. Saunders Company, 1936.

appearance of the macrophages, therefore, marks a secondary phase of intensified proteolysis. It is possible that this is followed by a tertiary phase during which the longitudinal channels are held open by endoneurial fluid seeping in the proximo-distal direction. This point, however, requires further examination. It is noteworthy that when a long tube of artery is attached to the end of a proximal nerve stump, with the free end ligated, it is found to be filled with fluid on the second day. When drained, the fluid is reformed. It has been observed as late as nineteen days after the operation.

The most remarkable feature of the liquefaction processes is that they spare that part of the fibrin network which has been oriented longitudinally under the influence of tension. Evidently this longitudinal fiber system is somehow protected against the proteolytic erosion. How this protection is achieved is still unknown. Two possibilities come to mind. The protection may be only apparent, in that the persistence of these fibers might merely be a result of their much larger size. In this case, all fibers would be attacked by the fibrinolytic enzymes indiscriminately, but the heavier ones would last longer, and the period of about one week, during which they serve as climbing ropes for the pioneering cells and fibers, would be insufficient for their complete dissolution. The other possibility is that the tensional orientation may have forced the surface molecules of the longitudinal fibrils into a more orderly and closer packing, which would provide fewer loopholes for the entry of proteolytic enzymes into the bodies of the fibers.

By the combined effects of tension and fibrinolysis, the framework of the nerve stumps has been rewoven throughout the former gap. The connecting fibrin threads now serve as guides for the outgrowing sheath cells and axons.

CELL INVASION

Ever since the classic experiments of Harrison ²⁰ in tissue culture, the tendencies of cells to glide along fibrous structures have been known. The precise mechanism by which cells, and nerve fibers as well, are made to glide along surfaces is not known, but present evidence indicates that interfacial tensions are operative.⁸ Our observations merely reaffirm earlier experiences. With the utmost clarity, the pioneering sheath cells can be seen to move from the nerve stumps into the union tissue along the fibrin fibers which they encounter at the very exits of the old nerve tubes. As we have previously said, these fibrin fibers are firmly anchored at the orifices of the neurilemmal tubes, and the emigrating sheath cells can therefore glide on into the scar along uninterrupted rails. Sheath cells emerging from the opposite nerve end behave similarly. As a result, the union tissue becomes populated with longitudinal, parallel, unbranched strands of sheath cells, with macrophages and occasional endoneurial cells interspersed (figs. 6*B*, 7*B* and 10*B*). Lack of branching of these cell strands may be ascribed to the same general principle established for nerve fibers, namely, that branching does not occur unless there is an incentive for it. Straight and unobstructed pathways offer no such incentive, and thus the sheath cells pass on straight from one stump to the other.

Evidently, sheath cells moving out from either end cease to migrate and proliferate as soon as they have made contact with similar cells coming from the opposite end. Whether it takes protoplasmic fusion or whether mere surface contact is sufficient to stop further growth seems irrelevant in the present connection. The main fact remains that the presence of straight guide lines between the two stumps insures that practically all sheath cells will be led head on against other sheath

20. Harrison, R. G. The Reaction of Embryonic Cells to Solid Structures. *J. Exper. Zool.* 17:521, 1914.

cells, thereby terminating growth in that particular line. In the end there will be just straight, simple bands of sheath cells connecting the two stumps (fig. 10 B), and no trace of the extensive gliomas so commonly found around nerve stumps.²¹ By the same token, the formation of neuromas by the regenerating axons of the proximal stump is averted. The very fact that the mechanism: tension \rightarrow fibrin orientation \rightarrow tissue growth, operates equally well in the presence or absence of neurites guarantees that *sleeve-splicing between a graft and a peripheral nerve stump* will leave no distal suture scar but will establish smooth and straight pathways for the later passage of nerve fibers from the graft into the periphery (fig. 10 A).

AXON REGENERATION

By the time the axons of the proximal stump have recovered from their ascending traumatic changes and are ready to grow out anew, the main guiding features of the union tissue have already been laid down and the outgrowing fibers find a straight and direct pathway to the peripheral stump all prepared. This pathway is still composed in part of the old fibrin matrix, but in part it consists already of strands of sheath cells. As was mentioned previously, the new axons grow preferentially along the sheath cell strands, although free advance has been observed sporadically.

There is no indication that nerve fibers and sheath cells are guided toward each other by specific attractions, and in fact there is much evidence against such a view.¹⁵ On the other hand, it is quite evident that as soon as axon and sheath cell are in contact, they tend to stick together. To quote a remote analogy, there is no force of attraction between a dry thread and a wet thread, but once both have come together, they stick. It seems that this is all that is needed to explain the association between nerve fiber and sheath cell if we keep in mind that the regenerating axons have never actually lost contact with sheath cells, as both are enclosed in a common neurilemmal tube. Therefore, if a regenerating sprout were to proceed into the scar independently, it would first have to detach itself from the sheath cell processes to which it adheres. As this detachment is apparently difficult to achieve, most axons stay in contact with sheath cells. It is possible, moreover, that specific mutual contact affinities⁸ between sheath cell and axon make this adhesion firmer than would be that between an axon and another type of cell.

The regenerating axons seem to glide with great ease along the surface of the sheath cell strands, for club-shaped enlargements of the axon tips, indicating damming of axonal substance before an obstruction, are very rarely seen in the union tissue of a successful sleeve-splice. The frequency of terminal axon swellings is in direct proportion to the obstructiveness of the scar, and their lack indicates unimpeded outgrowth. Pioneering fibers have been found advanced as far as 8 mm. from the level of regeneration on the eighth day. Allowing four days for the early reconstruction phase, this would indicate a growth rate of 2 mm. per day, including growth through the "scar."

Branching, which is as much a function of obstacles across the path of growth as is the formation of terminal bulbs, has likewise remained at a minimum. Whatever little there is occurs during the earliest phase of outgrowth, when the longitudinal fibrin strands still carry side connections. Axons sometimes bifurcate at the crotches, with one branch following the main stem, while the other turns off along

21. Dustin, A. P.: Les lésions posttraumatiques des nerfs: Contribution à l'histopathologie du système nerveux périphérique chez l'homme, *Ambulance de "l'Océan"* 1:71-161, 1917. Nageotte.⁶

the side branch. The fact, however, that little evidence of such axon branching is seen after the fifth day, indicates that the progressive resorption of the transverse fibrin threads, robbing nerve twigs attached to them of their support, must also have entailed the resorption of those axon collaterals. Only the straight fiber stem would thus be left to survive, or perhaps the vigor with which the nerve fiber advances in the main longitudinal direction drains growth requirements from the less vigorously growing collaterals and thus causes their atrophy. At any rate, the lack of branching can be definitely attributed to the orderliness of the preneural pathways. In contrast, branching in unspliced nerve unions or after faulty sleeve splicing is very profuse in accordance with the general disorganization of the scar.

The new nerve fiber tips of the proximal stump reach the level of the original cut surface usually several days later in sleeve-spliced stumps than in unspliced ones. This difference is explained by the fact that in the sleeve-spliced stumps the whole stretch of nerve inserted into the artery undergoes some traumatic degeneration. If this distance measures more than a few millimeters, it exceeds the normal range of ascending degeneration. The practical implications of this phenomenon would appear to be advantageous. It is a common experience that the segment lost by ascending degeneration is quickly repaired, inasmuch as the outgrowing fibers move unimpeded each in its own old tube. Consequently, their arrival at the nerve end would lag by no more than several days. On the other hand, their later arrival allows the union tissue more time to become organized and also gives the sheath cells, which move out from the level of section, a head start which they otherwise would not have. In fact, the more extensive ascending degeneration of the proximal stump may lead to the mobilization of a larger number of sheath cells than would normally be available at this end. It seems definitely more desirable to have the axons reach the gap only after the bed for their further growth has been properly prepared than to have them precipitated into the tangle of an early scar, which would leave marks of confusion in the restored nerve.

Our observations fully reaffirm the principle of contact guidance of the growing nerve fiber.⁵ This principle states that the course of a nerve fiber is determined by the biophysical and biochemical organization of the surfaces along which the fiber moves, which implies that nerve fibers can move in no other way than by application to interfaces. On the negative side, the principle denies that agents not in immediate contact with the nerve fiber can affect its course, except indirectly by modifying the contact substrata. There is no "attraction" of nerve fibers toward distant sources of chemical emanations, such as are postulated in the theory of neurotropism.²²

In spite of early opposition,²³ the theory of neurotropism has strongly influenced neurologic and surgical thought regarding nerve regeneration and nerve repair. The claim that degenerating peripheral nerve exerts a potent "attraction" on growing axons has been singularly intriguing. In view of the fact that surgical procedures based on this fallacious view are apt to be equally fallacious, it must be emphasized over and over again that this theory cannot stand up in the light of a critical evaluation of facts. To avoid repetition, we simply refer to previous

22. (a) Ramón y Cajal, S.: *La rétine des vertébrés*, Cellule 9:119, 1893. (b) Forssman, J.: *Zur Kenntnis des Neurotropismus*, Beitr. z. path. Anat. u. z. allg. Path. 27:407, 1900. (c) Tello, F.: *Gegenwärtige Anschauungen über den Neurotropismus*, Vortr. u. Aufs. ü. Entwicklgsmech. d. Organ., 1923, no. 33.

23. Dustin, A. P.: *Le rôle des tropismes et de l'odogénèse dans la régénération du système nerveux*, Arch. de biol. 25:269, 1910. Ingebrigtsen, R.: *Experimentelle Untersuchungen über freie Transplantation peripherer Nerven*, Zentralbl. f. Chir. 43:864, 1916.

presentations of the evidence by Weiss²⁴ and corroborative reviews by Harrison,²⁵ Detwiler²⁶ and Young.²⁷ The observations of Ramón y Cajal^{22a} and Forssman^{22b} that continuity is restored between severed nerve stumps even when the latter have been separated and brought out of line, are, of course, quite correct. However, this connection is effected not by "attraction" but by the influence of the stumps and their surroundings on the configuration of the union tissue, plus the fact that the earlier fibers making successful connections constitute a pathway of preferential application for fibers growing out later ("fasciculation").⁸

As a sample of additional evidence contradicting chemotropism in nerve growth, which will be reported more fully elsewhere, we cite the following experiment. A proximal nerve stump was inserted into the stem of a Y-shaped artery, with the fork offering alternative pathways to the regenerating fibers. A peripheral nerve stump was inserted into one of the open ends, while the other end was either left open or tied off or plugged with a piece of tendon. In no case were the regenerating nerve fibers "attracted" toward the peripheral nerve fragment, but the fiber stream divided itself more or less evenly and continued into both channels regardless of the kind of destination awaiting them.

Comparable observations were made in experiments mentioned previously, in which a proximal nerve stump was introduced into the end of a long arterial tube, the other end of which was ligated. This blind tube remained dilated first by blood, and subsequently by a liquid, composed presumably partly of fibrinolysate and partly of nerve exudate. There was a fibrin framework in the interior, much as in gaps between two nerve ends, and sheath cells and nerve fibers had grown in large numbers down the full length of the tube, only to be finally stopped at the blind end. They obviously grew toward no "destination," but simply along an established pathway with no exit. Growth in such arterial tubes is never as strictly oriented as it commonly is in sleeves between two stumps. Nevertheless, the main orientation is longitudinal. This may be attributed to the fact that adhesions of the ligated end of the arterial tube set the latter under longitudinal tension. Encouraged by these experiences, we are at present exploring the possibility of using stretched blood-filled sleeves in the role of grafts to bridge larger nerve gaps. This method would circumvent many of the shortcomings of the "tubulation" practices of the past.

FIBROSIS

Collagen formation in the union tissue sets in immediately after cell invasion. The role of the Schwann cell in this process has already been discussed. The earliest deposition of collagen in the otherwise fibrinous matrix appears along the surface of the Schwann cords. From there the process spreads into the interstices, establishing a new endoneurium. If it went no farther, collagenization would simply restore to the new nerve parts normal histologic features. However, in many instances it goes beyond limits compatible with the requirements of good nerve regeneration and nerve function. The result may be anything from moderate to serious fibrosis. The heavier the fibrosis, the denser the interstitial tissue will be; and the denser the tissue, the fewer nerve fibers will penetrate, the more will

24. Weiss (footnotes 8 and 15).

25. Harrison, R. G.: The Croonian Lecture on the Origin and Development of the Nervous System Studied by the Methods of Experimental Embryology, *Proc. Roy. Soc., London*, s.B **118**:155-196, 1935.

26. Detwiler, S. R.: *Neuroembryology*, New York, The Macmillan Company, 1936.

27. Young, J. Z.: The Functional Repair of Nervous Tissue, *Physiol. Rev.* **22**:318-374, 1942.

be prematurely arrested, the slower will be the advance of the successful ones, the less their ability to recover normal diameter and the greater their danger of becoming strangled and pressure blocked.

The arterial sleeve reduces the sources of fibrosis, but it does not altogether abolish them. It reduces fibrosis, first by shielding the interior from highly collagenous extraneural scar tissue, and second by turning whatever trace of fibroblastic tissue may have penetrated into the sleeve immediately into a longitudinal course parallel to the nerve, where it can do no harm. Naturally, these two protective features are predicated, the former on a hermetic seal between artery and nerve, and the latter on the presence of longitudinal stress. Accordingly, methods aimed at preventing fibrosis by tubulating or otherwise wrapping a nerve suture are apt to remain ineffective to the extent to which they fail to realize those two prerequisites. Yet, even with all extraneous sources of fibrosis excluded, there still remains the problem of intrinsic fibrous transformation, particularly of degenerated nerve. We have planned a special study of this problem and hope to be able to present tangible data at some later date. In the meantime, a few occasional observations deserve to be noted.

In a number of our cases, excess collagen was found in that portion of the distal nerve stump tucked into the arterial sleeve. The indications are that this represents a tissue reaction of the nerve to its compression by the sleeve. Compression is caused by the swelling of the peripheral stump during early degeneration (see figs. 1 and 2, Weiss,⁷ 1943), which amounts to tightening of the arterial grip. In response, the nerve produces new collagen. When limited to a short segment, this may be innocuous. However, it seems that some such hypertrophy of collagen may occur throughout the distal stump, possibly as a direct reaction of sheath cells and endoneurium to the increasing turgor of the degenerating fibers. The excellent nerve fiber growth commonly observed in peripheral stumps indicates that hypercollagenization of moderate degree is no bar to successful regeneration. Evidently, later shrinkage of the degenerated fibers, with or without reinnervation, removes the internal pressure, which if it were kept up might easily lead to progressive fibrosis. Extraordinary circumstances, however, may lead to just that, and it is worth investigating whether some instances of intraneural fibrosis may not be blamed on irregularities of the degeneration process, such as, for instance, delay in the resorption of the "ovoids," congestion of the tubes with hyperplastic sheath cells, etc. Continued research into the causes of fibrosis, it is hoped, will produce measures of nerve repair which are not only "afibrotic"—keeping fibrosis out—but also "antifibrotic"—counteracting it where it has occurred. Preserving a certain fluidity of the nerve spaces seems to be a prime factor of success. The role of the endoneurial fluid in maintaining this fluidity has been suggested⁷ but remains to be demonstrated.

Nerve grafts seem to be particularly susceptible to fibrosis, but without a detailed analysis it is impossible to give the reason for this change or to formulate possible means of averting it. Fibrosis of the densest sort is what makes alcohol-fixed nerve grafts unfit for use. While some nerve fibers may penetrate,²⁸ regeneration through the graft and its replacement tissue remains insignificant,²⁹ even though

28. Huber, G. C.: Operative Treatment of Peripheral Nerves After Severance, More Particularly After Loss of Substance: A Critical Review, *J. Lab. & Clin. Med.* 2:837-848. 1916-1917. Nageotte.⁶

29. Sanders, F. K., and Young, J. Z.: The Degeneration and Reinnervation of Grafted Nerves, *J. Anat.* 76:143-166, 1942.

the orientation of the tissue is of the required kind. We have convinced ourselves of this fact in experiments on the rat.

In conclusion, it can be stated that proper orientation of the matrix is not enough to insure optimal nerve regeneration; the matrix must also be of the right composition, and this includes a correct balance between collagenous and noncollagenous constituents.

CONCLUSIONS

In the light of our analysis, the arterial sleeve appears to fulfil a variety of functions.

1. It unites the nerve ends. However, the initial holding power of this link is not sufficient to withstand more than moderate tension. It could not maintain a forcible approximation of the nerve ends such as may be attempted for the reduction of a sizable nerve gap. In such cases, stay sutures at a safe distance from the nerve ends could be used to take up the main stress, leaving just enough stretch to keep the union taut. The presence of some blood-filled gap between the cut surfaces seems imperative.

2. The sleeve serves as container for the cementing blood clot.

3. By liquefaction along its inner walls, it prevents lateral adhesion of the union tissue. This throws all tensional stresses into a strictly longitudinal direction, thus bringing the fibrin matrix of the union tissue into alinement with the severed nerve fibers and creating a guiding pattern for the transit of cells and axons across the former gap.

4. The sleeve prevents the dissipation of the products of liquefaction, as well as of endoneurial fluid, and thus preserves a degree of fluidity optimal for nerve regeneration.

5. The sleeve prevents the ingrowth of extraneural connective tissue into the gap, as well as the escape of sheath cells and axons from the nerve. This it achieves not so much by grossly walling off the interior from the exterior, as by permitting a tissue matrix to form which will deflect all cell and fiber streams in the longitudinal direction.

6. This action likewise accounts for the lack of branching among the outgrowing axons and Schwann cords and for the suppression of the neuromas and gliomas which would otherwise develop.

7. The sleeve permits direct vascular reconnection between proximal and distal stumps through the gap, while excluding the intrusion of extraneural blood vessels. Whether there is any significance to this point remains to be determined.

These points constitute the crucial advantages of arterial sleeves. The list can serve a double purpose. Firstly, if the use of arteries should prove impracticable in man one could try to resort to composite procedures, i. e., substitute for the single action of the arterial sleeve a combination of measures, for instance, one providing for the sealing, another for the tension pattern, a third for liquefaction, etc. Secondly, the list establishes criteria by which the prospects of tubulation and wrapping procedures in nerve repair may be assessed. Unless such procedures score favorably when tested point for point down the list, they are not likely to measure up to the results hitherto obtained with arterial sleeve splicing. A survey of the literature on tubulation shows that many past procedures falling in that class bear only superficial resemblance to arterial sleeve splicing. None of them fulfils vigorously all requirements of our list. Some are excellent in one respect but fail in others. Practically all of them deprive the union tissue of the benefit of longitudinal tension. Others leave spaces between tube and nerve, perhaps small

in macroscopic terms but huge for cells which operate in microscopic dimensions. Still others introduce foreign substances, such as gelatin or agar-agar or air, into the gap, creating a situation diametrically opposed to what would aid the nerve. The idea that a medium will be favorable for nerve growth just because it is "soft" or "nutrient" or rich in vitamin B₁, etc., is based on a serious misconception of the mechanism of nerve growth. Such notions can usually be traced to the tempting analogy between a nerve sprout and a plant root. Yet nerve fibers decidedly do not grow after the fashion of plant roots. They grow by surface application, and the physical configuration of their matrix is as important as is the chemical composition of the medium.

To replace conjectures about the requisites of nerve regeneration by factual knowledge seems the only safe way toward the creation of a solid and rational basis for the improvement of nerve repair. The present article is presented as a contribution toward that goal.

SUMMARY

A study of the processes following the reunion of severed nerve ends by an arterial sleeve in the rat has revealed a typical sequence of events, as follows:

A blood clot cements the nerve ends.

Within a day the red cells break up, leaving the fibrin net of the plasma standing.

Owing to liquefaction along the arterial wall, the union clot becomes detached laterally, while remaining firmly fused to the nerve ends.

This results in longitudinal tensions transmitted from nerve to clot to nerve.

These tensions orient the fibrin fibers in longitudinal directions.

Proteolysis throughout the clot, beginning about the second day, gradually destroys all fibrin fibers except the ones oriented lengthwise. Thus a system of longitudinal fibrin strands bridging the gap from stump to stump is established.

Macrophages move into the gap, continuing the clearing of liquid channels. Sheath cells move out from both nerve stumps, glide along the fibrin rails and give rise to the deposition of endoneurial collagen on their surfaces.

Axons regenerate, mostly in application to sheath cells, along the same straight and direct guide lines. Lacking obstructions, they proceed essentially without branching.

The main framework of the nerve union is completed by the end of the first week, and subsequent developments concern mainly the utilization of the bridge by increasing numbers of nerve fibers and the maturation of the latter.

These experiments have established a number of conditions prerequisite for optimal nerve regeneration. They point the way toward the avoidance of confused suture lines, neuromas, gliomas and nerve fibrosis. Even if the arterial splice as such should not be applicable in clinical practice, the lessons learned from this analysis of its merits may guide the search for improved methods of nerve repair.

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EVALUATION AND TREATMENT OF FACTORS INVOLVED IN POSTLOBECTOMY COLLAPSE OF THE LUNG

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The initial stage in the surgery of pulmonary resection has now passed. In the pulmonary as in every region of the body when emerging within the scope of surgical intervention, operation carried with it a high mortality rate. But in the last decade the rate associated with lobectomy has steadily declined from 50 per cent to an average of 10 per cent, and it is even as low as 2.5 per cent in certain clinics for patients with diseases of the chest. Now the emphasis has shifted from the immediate risk of resection of a progressive and eventually fatal lesion to the securing of the maximum postoperative function for the patient. Actually today both these problems are one, namely, the prevention of postoperative collapse of the lung.

CAUSATION OF POSTLOBECTOMY COLLAPSE OF THE LUNG

Collapse of the lung after lobectomy is of two distinct types, depending on whether the involved lobe shows complete or incomplete airlessness.

The complete form, or apneumatosiis, is caused by conditions which prevent the circulation of air while maintaining the circulation of the blood in any area of the lung. The collapse is due to the elastic recoil of the lung as the entrapped air is absorbed into the blood stream, while the loss of further aeration may be produced either by complete bronchial obstruction from an intraluminal block or by bronchiolar obstruction due to pressure from without, such as a pleural effusion which abolishes both the intrapleural subatmospheric pressure and the cohesion of the visceral to the parietal pleura.

In the second, and more common, form there is lack of expansion of the remaining lung tissue to fill the thoracic cavity, though occasionally this is due to inadequate compensatory distention. This form of collapse may be produced by fibrosis following inflammation of the lungs and the pleura. But to be of much consequence the process must be diffuse, for a local lesion is readily compensated for by increased distention of the healthy lung tissue. Other factors also are credited with the production of this form of collapse. For instance, alteration in the vascular supply to the lung has a definite effect. Ligation of the pulmonary artery is followed by shrinkage and collapse, with fibrosis of the corresponding part of the lung. Ligation of the bronchial arteries produces no effect, but if it is combined with ligation of the corresponding pulmonary artery, gangrene ensues. Ligation of the pulmonary veins is followed by stasis and engorgement; these may be lethal, though the collateral return usually suffices. It has been repeatedly stated that there is a reflex form of collapse, but there does not appear to be any conclusive evidence of it. That such collapse is not due to paralysis of the muscles of respiration is shown by the numerous patients with phrenic evulsion and intercostal neurectomy who do not have collapse of the lung. It has been suggested

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that reflex collapse is produced either by bronchial spasm or by angioneurotic edema, but clinically and experimentally both these conditions are found to lead to emphysema and never to collapse, as complete obstruction does not occur from these factors alone. Factors of unknown importance in the collapse of a lung are those of interpleural surface tension and cohesion. Apparently they account for the fact that the lungs do not collapse when the intratracheal pressure is made considerably less than the intrapleural pressure, but their precise role is so far undetermined.

At present the known factors in the production of postlobectomy collapse are bronchial obstruction and fibrosis, and the latter may be caused either by infection of the remaining lobes or by operative trauma to their arterial supply through the pulmonary arteries. Clinically, collapse after lobectomy appears to be of three main types (Churchill¹). The first type is due to the pressure of an encysted collection of fluid, which is usually apical in position. The second type is massive collapse. This is due to bronchial obstruction, and the affected lobe is almost invariably found to be adherent to the wall of the chest. And the last type, which I think is the most common and certainly is the most dangerous, is due to chronic progressive infection of the lobe with subsequent diffuse fibrosis. The fibrosis probably starts around areas of destruction of tissue in the bronchioles. However, it may be due to growth of granulation tissue into a long-standing alveolar exudate, the stasis being due either to inadequate vascular and lymphatic absorption or to deficient bronchial drainage.

The infection must be diffuse. I had a patient in whom the lower lobe of the left lung was resected for bronchiectasis and six weeks later an abscess developed in the nearly expanded upper lobe with resultant complete collapse. After drainage of the abscess expansion took place and only a small thoracoplasty was needed to complete the cure. At the time of writing he has remained well for over a year, can walk 10 miles (16 kilometers) without fatigue and has negligible cough and sputum.

It is especially to prevent chronic progressive infection, that meticulous care must be taken in the handling of the patient. In fact, evaluation and the treatment of factors involved in postlobectomy collapse require a survey of all the possible causes of bronchial obstruction and of pulmonary infection and fibrosis together with their treatment in the preoperative, the operative and the post-operative management of a patient.

PREOPERATIVE STAGE

Before operation an estimate of the degree of fibrosis already present in the lung and hence of the postoperative chance of incomplete expansion and the need for thoracoplasty can be made from the history and the roentgen examination. The majority of patients suitable for lobectomy have recurrent attacks of pneumonia, and it is my impression that if these attacks are limited to the proposed area for resection the prognosis is far better than if other lobes are involved as well. A more reliable estimate can be made during bronchographic examination, when the degree of movement at the interlobar regions can be observed. If movement is markedly diminished, it is almost certain that fibrosis has spread through the interlobar septum and involved the apparently unaffected lobe, with consequent increased risk of its postoperative collapse. I find this is better observed by screening than

1. Churchill, E. D.: Personal communication to the author, 1941.

by the study of bronchograms taken in different phases of respiration, and I consider it of more prognostic significance than the degree of atelectasis of the diseased lobe. In fact, I have been unable to find any definite relation between the degree of preoperative atelectasis of the diseased lobe and the postoperative expansion of the remaining lung tissue, though such a relation is frequently assumed to exist.

In the routine methods employed for the diagnosis of pulmonary lesions there appears to be an element of risk. The insufflation of powder does not give satisfactory definition unless the bronchial tree is practically dry; in view of this, iodized oil has been introduced. Iodized oil gives excellent bronchograms, but from time to time there have been reports of pneumonia following its use, and it

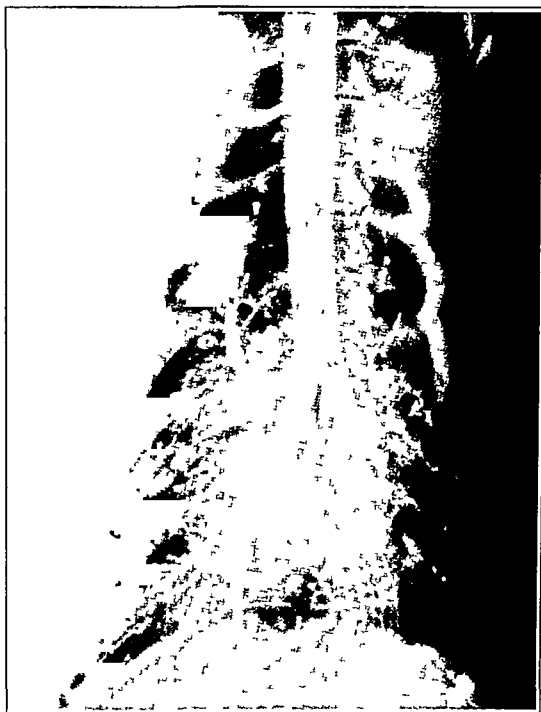


Fig 1.—Bronchogram taken nine days before death showing that the lower lobe of the left lung has been removed and that the animal is not suffering from a drowned lung.

has been suggested that it is a cause of postlobectomy collapse (Belsey²; Gowar and Gilmour³).

To obtain controlled evidence of its effect, 25 cats were used. Rabbits were not employed because their physiologic makeup is so different from that of man; for instance, they cannot cough. The cats were anesthetized with appropriate intraperitoneal doses of pentobarbital sodium; an intratracheal catheter was passed, and amounts up to 5 cc. of iodized oil (3 different preparations were used) were injected. Small amounts of cocaine were sometimes injected before the iodized oil, but this made no difference in the results. Roentgenograms were taken to show the accuracy of the injection, and the animals were examined postmortem from one day to thirty-two weeks afterward. Some of the animals were subjected to

2. Belsey, R. H.: Brompton Hosp Rep. **6**:133, 1937

3. Gowar, F. J. S., and Gilmour, J. R.: Brit. J. Exper Path. **22**:262, 1941.

lobectomy in the interim. Three had a second injection by the same method: 2 were given the second injection six weeks after the first, and in the case of the third eleven weeks elapsed between the injections. One cat had three injections: the two later injections were given two and eight weeks after the first introduction of iodized oil.

Lipid pneumonia occurred in 3 of the cats.^{3a} The first had had one injection of iodized oil and died of anoxia four weeks later, immediately after lobectomy. One lobe showed small areas of lipid pneumonia. The second cat had the first injection four weeks before excision of the lower lobe of the left lung and the second injection two weeks after the operation. Five days later the animal was cyanosed and not eating. On the ninth day after injection, being moribund, it was killed with chloro-



Fig. 2.—Photograph of the right lung showing the typical pale yellow areas of lipid pneumonia.

form, and large areas of collapse due to lipid pneumonia were found in all the remaining lobes. The third cat also had the first injection four weeks before excision of the lower lobe of the left lung and the second injection two weeks after operation. It died of diffuse lipid pneumonia two weeks later.

No relation was observed between the length of time iodized oil remained in the lungs and the onset of lipid pneumonia; roentgenograms showed large quantities in some animals for as long as a month without any untoward effect. No other histologic change was found that could be attributed to iodized oil. Whether such a condition plays any part in postlobectomy collapse in man is doubtful. With Mr. J. E. H. Roberts' permission I have been able to examine the notes and roentgenograms of 50 of his cases at the Brompton Hospital, London, England.

^{3a} Chesterman, J. T. *J. Path. & Bact.* 54:385, 1942.

I can find no relation between the dates of administration, the number of administrations, the quantity of iodized oil used, the amount of iodized oil still present in the lungs at the time of operation as shown by roentgenograms and the extent of postoperative collapse of the remaining lobes. In this connection it is worth noting that postoperative collapse on the side not operated on is rare, occurring in only 2 of 51 cases of collapsed lobe in Tudor Edwards' series cited by Gowar,⁴ though bronchograms had been made of both lungs.

In order to minimize the risk of postoperative infection it is essential that retention of secretions in the respiratory passages be avoided. Nasal sinusitis should be treated by adequate drainage, but radical procedures should not be resorted to until after the extirpation of the pulmonary lesion, for the continual coughing of purulent sputum makes the eradication of nasal sepsis impossible.

For drainage of the bronchi the most common method is postural drainage, but this to be effective must be practically continuous, since any relaxation of position allows repooling to take place. Its main value is for children, whose cough



Fig. 3.—Roentgenogram of the right lung showing iodized oil present in the areas of lipid pneumonia.

is often ineffectual and who can be maintained in the correct position for twenty-three hours a day. In the treatment of adults it is useful for short periods after an exacerbation of infection, but bronchoscopic aspiration, repeated if necessary, is far more effective, for it breaks up and removes the viscid secretion which collects in the dilated bronchi, and it stimulates coughing by its mechanical irritation.

The most satisfactory routine method appears to be the use of the creosote chamber, which increases expectoration by the physiologic method of stimulating the cough reflex. I have subjected mice to concentrations of vaporized creosote B. P. six times stronger than that used for human beings for four hours a day and six days a week and found no ill effect discernible either by the naked eye or on microscopic examination of a section of the lungs taken at necropsy up to fourteen weeks from the onset of treatment.

The method adopted should be continued until there is no further decrease in the amount of sputum voided and for at least a month after the last attack of infection of the respiratory tract has subsided.

4. Gowar, F. J. S.: *Brit. J. Surg.* 29:3, 1941.

My impression is that patients with an efficient cough reflex as shown by the rapid expectoration of iodized oil are less liable to suffer from postoperative infection than others whose processes of elimination are less satisfactory.

The preoperative attempt to prevent collapse by the formation of adhesions between the visceral and the parietal pleura has attracted considerable attention, for if fusion of the pleura in given areas could be produced safely, it would prevent both any movement of the mediastinum during the operation and the complete collapse of the remaining lung tissue afterward.

Many methods and agents have been used to induce this condition (Bethune⁵; Singer⁶; Hanrahan, Adams and Klopstock⁷; Gowar and Gilmour⁸). I have tried silver nitrate, zinc sulfate, iodized talc and benzomastic. The last-named compound produces no apparent reaction, and of the two others silver nitrate produces in both cats and rats marked pleural effusions (unless used in a concentration sufficient



Fig. 4.—Low power photomicrograph of an area of lipid pneumonia, also showing normal lung tissue and pleura.

to damage the parenchyma of the lung) when adhesions are formed, but necrosis and death also may occur. Zinc sulfate, too, is variable in the reaction it causes.

Talc powder containing 0.5 per cent iodine has been found the most reliable agent by the majority of workers, and the results of its use have been studied in 22 cats. These were anesthetized by intraperitoneal administration of pentobarbital sodium, and in 17 poudrage was performed, either by blind insufflation through a small intercostal incision or under direct vision with a larger incision, the object being to fix the upper lobe. The method did not appear to affect the result, for all 5 cats killed in the first three days after poudrage showed a uniform diffuse distribution of the powder in the pleural cavity. After a week the powder was

5. Bethune, N.: *J. Thoracic Surg.* 4:251, 1935.

6. Singer, J. J.; Jones, J. C., and Tragerman, L. J.: *J. Thoracic Surg.* 10:251, 1941.

7. Hanrahan, E. M.; Adams, R., and Klopstock, R.: *J. Thoracic Surg.* 10:284, 1941.

8. Beecher, H. K.: *Acta med. Scandinav.*, 1938, supp. 90, p. 146; *J. Thoracic Surg.* 10:202, 1940.

mainly found on the mediastinal surface aggregated into small collections. Adhesions may commence to form on this aspect as early as the fifth day.

Excision of the lower lobe was performed on 7 animals on the fourteenth day. Three showed firm adhesions round the upper lobe, while the lower lobe was practically free; 2 showed marked mediastinal adhesions of both lobes; 1 showed marked basal adhesions only, and 1 showed both basal and apical adhesions. Thoracotomy performed on or after the twenty-first day showed firm adhesions of part or of the whole of the lung to the surrounding structures in every case. This confirms previous observations that iodized talc produces adhesions but that the position and the extent of these cannot be controlled. In estimating the result of this aseptic pleuritis it is necessary to consider the effect of the iodized talc on the pleura and the subjacent lung and also the effect of the adhesions thus produced on the postoperative expansion of the remaining lobes.

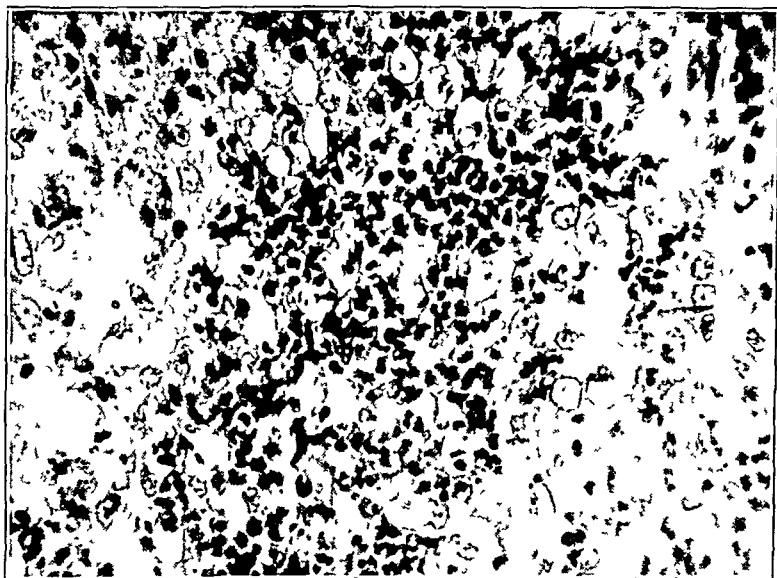


Fig. 5.—High power photomicrograph of an area of lipid pneumonia showing phagocytic cells containing large globules of lipid, proliferation of cells in alveoli and a polymorphonuclear response.

As far as could be judged there was no toxic effect after insufflation of the powder, which at the end of a week tended to agglomerate and give rise to focal reactions with fibroblastic proliferation, a macrophage response and occasional giant cells. The subjacent lung did not appear to be in any way affected, nor could crystals be seen in the pleural and superficial pulmonary lymphatics. No involvement of lymph glands was seen.

The effect of these adhesions on the lung have been studied both before and after lobectomy. Of 9 cats examined before operation, between two and six weeks from the date of poudrage, 1 showed 50 per cent collapse of the upper lobe, which was bound down by the artificially produced adhesions. In the postoperative series 2 animals examined (one eight weeks and the other sixteen weeks after operation) were found to have the remaining lobe of the same size as before operation, adhesions having prevented compensatory distention. One animal, examined ten weeks after lobectomy, showed irregular expansion of the upper lobe with areas of emphysema and areas of collapse due to contraction of the adhesions.

A fourth animal, fifteen weeks after operation, showed diffuse fibrosis of the remaining lobe, which was firmly adherent to the apex of the thoracic cavity, and a fifth animal, eight weeks after operation, showed practically complete collapse of the remaining lobe. This lobe was then freed, and at necropsy, eight weeks after the pneumonolysis, it had reexpanded and practically filled the left hemithorax.



Fig. 6.—Low power photomicrograph of a typical adhesion produced by talc and iodine poudrage.

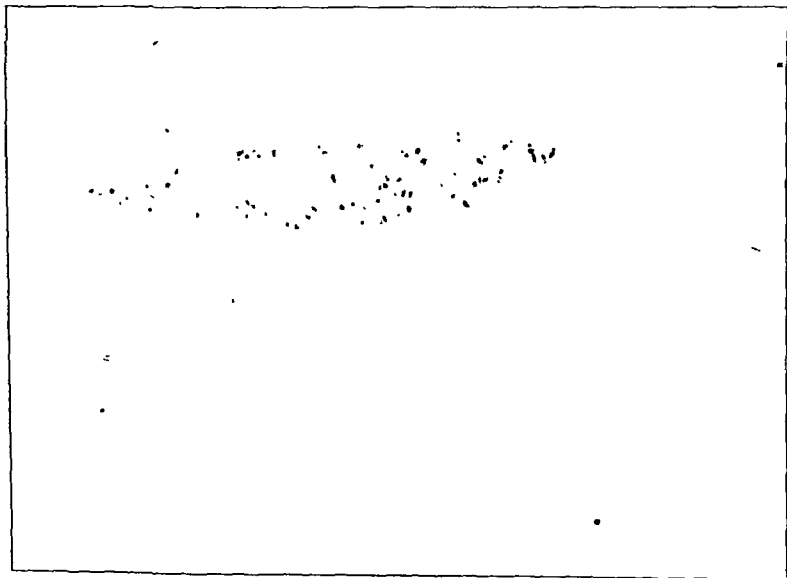


Fig. 7.—With addition of a Nicol prism showing the reaction is around the crystals of the talc powder.

In none of these animals was there found any evidence of bronchial obstruction, and the affected side was filled by mediastinal shift with which hernia of the opposite lower lobe was sometimes associated.

Of the 5 cats treated by the injection of a suspension of the powder into an artificial pneumothorax cavity, two showed no adhesions at two and three weeks

respectively, 1 showed marked mediastinal adhesions which made lobectomy difficult at the sixteenth day, and the other 2 had formed adhesions by the fourteenth and sixteenth day which made excision of the lower lobe impossible.

Adhesions were found after the injection of a suspension in isotonic solution of sodium chloride but not when sterile water was used.



Fig. 8.—Photomicrograph showing typical emphysema.

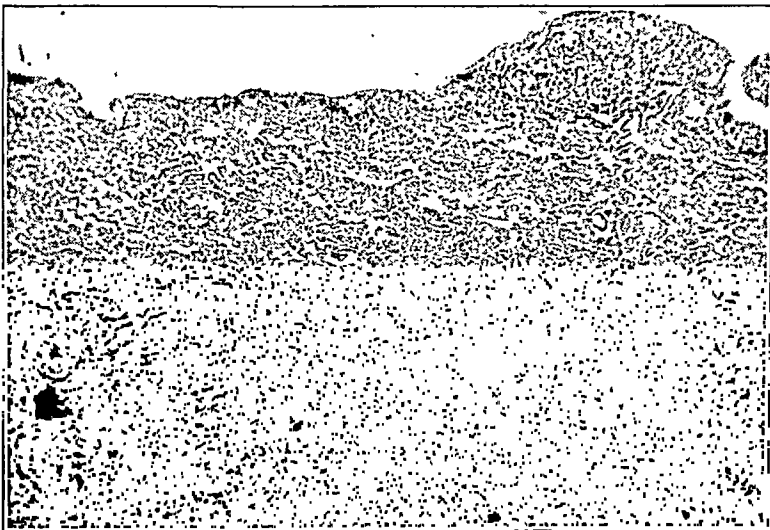


Fig. 9.—Photomicrograph showing typical collapse (same power magnification as in figure 8) taken from the same lobe at a distance of 1 cm., illustrating the effect of artificially produced adhesion on the expansion of the lung after lobectomy.

From these experiments there can be no doubt that with iodized talc poudrage: (1) adhesions can be produced but their situation and elasticity cannot be controlled; (2) the aseptic pleuritis produced gives rise to no ill effect on the parenchyma of the lung; (3) adhesions so produced are capable of causing dis-

tortion of the lung before operation and of causing collapse which may be permanent and complete in the remaining lung tissue of the same side after lobectomy. There is considerable difference of opinion regarding its use in man. Some surgeons hold that poudrage has greatly lessened the risk of postoperative collapse in their cases, while others consider it inadvisable because of the risk of empyema complicating the method and also because of the degree of thoracic deformity which follows when one side of the chest is not completely filled with lung tissue. For if pleural fusion is attained the remaining lobe cannot fill the normal hemithorax. The statistics of the two groups are not convincing in either direction, and it may be that the improvement of results of those in favor of poudrage is due to other factors.

As Churchill¹ has pointed out, the essential features to note are that pleural adhesions do not prevent a chronic progressive infection leading to fibrosis and collapse and that cases of bronchial obstruction with massive collapse are nearly always associated with adhesions to the wall of the chest. This suggests that in man the bronchial obstruction may be directly due to adhesions.

ANESTHESIA

The essentials of anesthesia for resection of a lung are the prevention of anoxia, the control of secretions and the abolition of reflex disturbance (Beecher⁸).

The following method is simple and satisfactory: A mixture of hydrochlorides of opium alkaloids (omnopon; pantopon) $\frac{1}{3}$ grain (0.02 Gm.) and scopolamine $\frac{1}{150}$ grain (0.4 mg.) are given one hour before operation, and the patient is then left in a darkened anesthetic room with a $\frac{1}{2}$ grain (0.03 Gm.) decicain (tetracaine hydrochloride) lozenge in his mouth. Just before removal to the theater an intratracheal catheter of about one third the diameter of the trachea is passed with a laryngoscope and the preoperative medication is repeated together with administration of ephedrine. The patient is then placed in the lateral position on the table, which is tilted with a 10 degree slope, head downward, and as a spinal anesthetic 1:1,500 hypotonic solution of nupercaine hydrochloride is given. The intratracheal catheter is then connected with oxygen flowing at the rate of 2 liters a minute and attached to a valve so that a greater pressure than 1 cm. of mercury cannot occur. At a moment's notice the intratracheal catheter may be disconnected from the oxygen and attached to an electric aspirator which is kept in readiness. The intratracheal catheter is well tolerated, and besides supplying oxygen and being available for aspiration, it makes coughing ineffectual, thus preventing the dissemination of infected material in that way should flooding occur. Preoperative measures rarely empty a pathologic lobe of all its secretion. Since unfortunately bronchial tampons are difficult to insert and liable to displacement during the operation, reliance must be placed on intratracheal aspiration and posture to prevent the dangers of obstruction to the airway and the dissemination of septic secretions should flooding take place. It can be shown by injecting iodized oil into a lower lobe and placing the patient with that side uppermost in the position already described for lobectomy together with an intratracheal catheter in position, that dissemination is definitely less in the conscious patient than in one under general anesthesia. For at some period of general anesthesia there are irregular respiratory movements which do not occur in the conscious patient, and this is particularly so when the anesthesia has to be stopped to allow aspiration. The intratracheal oxygen prevents anoxia and does away with the risks of positive pressure anesthesia, such as impaction of secretions

in the smaller bronchi with subsequent atelectasis and infection and also the risk of alveolar rupture and the alteration of normal gaseous interchange due to failure of the expiratory muscles. It also avoids the manifold intricacies of controlled respiration and the danger involved in the lowering of the carbon dioxide content of the blood inherent in this method. This depletion of carbon dioxide so alters the dissociation curve of oxygen that a patient may appear to be of satisfactory color when definite tissue anoxia is present.

Marked increase of the carbon dioxide content of the blood also is deleterious, as it leads to cardiac irregularity and death from dilatation of the heart even when pure oxygen is being breathed (Crafoord⁹). The intratracheal administration of oxygen prevents lack of oxygen in the blood, even when both pleural cavities are open simultaneously, but in unawareness of the effect on the alkali reserve of the blood of prolonged open pneumothorax when intratracheal oxygen is being administered, the following experiments were performed: Six cats were anesthetized with intraperitoneally administered pentobarbital sodium. The left side of the chest was kept wide open for three hours in 4 cases and for two and a half hours and one hour in the other 2 animals, while oxygen was given intratracheally at a rate of 2 liters a minute and at a pressure not above 1 cm. of mercury. Blood was taken from the left ventricle at once and at regular periods afterward, and no alteration in alkali reserve was found, though 2 animals were subjected to total pneumonectomy, 2 previously had had single lobes removed and 2 had simple thoracotomies. Two further animals were tried. One was deliberately and grossly overdosed with anesthetic and died shortly after the three hour period with a 30 per cent rise in the alkali reserve. The other animal died at two and three-quarter hours with the same findings, but it had had both lower lobes removed and the upper lobe of the left lung was completely fibrosed, so it had considerably less functioning lung tissue than would occur in an operation on man.

A local anesthetic is never injected into the hilar region, for evidence is accumulating that paralysis of the vagal branches to the lung may tend toward postoperative pulmonary edema, especially if fluids are given intravenously (Farber¹⁰). O'Shaughnessy¹¹ showed that blocking the vagus at the hilus did not abolish cardiac irregularity, and Edwards¹² found no evidence of hilar reflexes and demonstrated that their alleged effect was produced by mechanical obstruction through torsion of the main pulmonary artery. Certainly there has never been any need to invoke such reflexes to account for the condition of the patient in any operation I have seen.

OPERATIVE STAGE

Operation should be performed after midday, so that any accumulation of secretions can be expectorated during the morning. The importance of this in pulmonary tuberculosis has long been known (Allen¹³), and I believe it applies equally whenever there is the complication of excessive sputum.

During the operation it is rare to find anything like a complete fissure dividing a pathologic lobe from its neighbors, and the separation is best carried down to the hilus by incision and immediate closure. Blunt dissection lacerates the lung and makes suture more difficult and so increases the risk of bronchopleural fistula.

9. Crafoord, C.: *J. Thoracic Surg.* **9**:237, 1939.

10. Farber, S.: *Neuropathic Pulmonary Edema: Further Observations*, *Arch. Path.* **30**: 180 (July) 1940.

11. O'Shaughnessy, L.: *J. Thoracic Surg.* **5**:386, 1936.

12. Edwards, R.: *Brit. J. Surg.* **27**:392, 1939.

13. Allen, D.: *J. Thoracic Surg.* **4**:76, 1934.

with its attendant alterations in intrapleural pressure and with the formation of a pathway for the spread of infection in either direction.

The method of dealing with the hilus must reduce the incidence of such fistulas to a minimum. Also, it must not produce more than a minimal reaction in the bronchus, especially if the upper lobe is being excised, for fear of obstructing the main stem bronchus. And, finally, care must be taken in the ligation of the blood vessels, as occlusion of a large branch of the pulmonary artery running to another lobe is easy and may lead to fibrosis in its area of supply, while sepsis in the pulmonary vein may lead to retrograde thrombophlebitis and collapse of the adjacent lobe. Fifteen lobectomies have been performed on cats and the effects studied from a few hours to six months after operation. Some were performed by individual ligation; some, by mass ligation, and others, by various combinations, and in this small series the results were equally satisfactory whatever the method employed. In man dissection of the pedicle with the application of a clamp is to be avoided unless suture is possible well proximal to the clamp, as crushing of the cartilage usually leads to fistula formation. It would appear from the careful work of Blades¹⁴ that individual ligation is the best method so far devised. But if this is not practicable, then the tourniquet must be resorted to, and it should not be placed too close to an adjacent lobe for fear of occluding branches of the pulmonary artery running to it. Inflammatory reaction is limited by placing as few sutures as possible in the stump before removing the tourniquet. If speed is essential, the application of two tourniquets on the proximal side allows first one to be loosened and tied and then the other without the necessity of any sutures. Sloughing does not appear to take place, and fistula is rare after this procedure.

The phrenic nerve should not be interrupted during the operation, as this interferes both with inspiration and with the reciprocal innervation of the muscles used in coughing and so further lessens the power of expectoration in a chest already suffering from lack of adequate intercostal movement consequent on thoracotomy. Phrenicectomy also predisposes to collapse by increasing the intrapleural pressure (Haight¹⁵).

On the evidence already presented I suggest that any adhesions found running to the remaining lung tissue after lobectomy be carefully scrutinized and sectioned if it appears that by their contraction they will distort the bronchus or lead to irregular expansion of the lobe. I have had 1 man whose case I think illustrates this point. At the removal of the lower lobe of the left lung great care was taken not to divide the adhesions running from the upper lobe to the diaphragm. After operation the lobe appeared to be pulled downward and expansion took place from below up and was not complete for about fifteen weeks.

Lobectomy is an operation which is difficult to perform without soiling the operative field; so antiseptics are frequently employed. As the effect of many of these substances on the pleura and the subjacent lung was unknown, the following experiments were performed to ascertain if they had any relation to postoperative collapse.

1. One cubic centimeter of a 1:1,000 aqueous solution of euflavine was injected into the pleural cavity of rats. Necropsy was performed at varying periods up to ten weeks, and no histologic change was found. The dye staining was no longer visible to the naked eye after a fortnight.

14. Blades, B., and Kent, E. M.: *J. Thoracic Surg.* **10**:84, 1940.

15. Haight, C., and Deegan, J. K.: *Am. Rev. Tuberc.* **25**:197, 1937.

2. Ten milligrams of sodium sulfathiazole in 10 per cent solution in isotonic solution of sodium chloride was injected into the pleural cavity of normal albino rats 100 to 150 Gm. in weight. A slight pleural effusion formed at once but was reabsorbed in forty-eight hours, and no histologic change was found at autopsy from the second to the fourteenth day. If large doses were given, pleural effusions rapidly formed and the animals died with cyanosis and dyspnea.
3. Ten milligrams of sulfathiazole in a 10 per cent suspension in 6 per cent acacia in isotonic solution of sodium chloride showed a slight pleural effusion for four days, but otherwise no change.
4. Sulfapyridine in the same dosage and in a similar suspension produced no definite effect to the naked eye or on biopsy up to seventeen days from injection.
5. Neither the rats given injections of the suspending medium nor the controls showed any change.

From this I think it may be inferred that euflavine in normal concentrations does not affect the pleura or the lung, that sulfathiazole and sulfapyridine are also innocuous in average doses but that the former should not be placed in the pleural cavity in large quantities as it causes massive effusion, though not so readily as does sodium sulfathiazole. I always use cloths wrung out in euflavine solution to protect the edges of the wound, but I have never at operation placed any of the sulfonamide compounds in the pleural cavity, as the organisms found in putrid empyema due to opening of the bronchus are not affected by this group of drugs. This form of empyema may lead to collapse from fibrosis of the visceral pleura, which is rare in other septic infections if they are adequately drained.

Drainage is not a necessity after lobectomy, but I feel that it is like Moynihan's hypnotic stitch; the surgeon sleeps the better for its use and the patient need in no way be inconvenienced by it. If in some cases the surgeon feels that it can be dispensed with, I think it is advisable to leave a little sodium citrate solution in the pleural cavity to retard coagulation, for in cases in which clot forms aspiration is difficult and usually ineffectual and more adequate drainage has to be established. The site of drainage should be posterolateral, and it should not be dependent, as this leaves a long sinus track when the diaphragm rises. I have found intercostal drainage satisfactory, and there is no need with modern methods of dealing with the hilus to insert the tube more than just through the wall of the chest.

POSTOPERATIVE STAGE

The tube should be attached to an apparatus so that known definite degrees of negative pressure can be maintained in the thorax during normal respiration but so that forceful expiration and coughing will take place against a known definite positive pressure.

The importance of this is obvious on reflection on the mechanism of removal of material through the respiratory passages. Ciliary action and respiratory movement aid, but coughing is the essential way. The tussive squeeze forces secretions into the larger bronchioles, and from those of 1 mm. in diameter or over the bechic blast, which is formed by the sudden opening of the glottis following a rapid increase of intrathoracic pressure, forces a column of air from the alveoli

to the exterior (Archibald and Brown¹⁶; Carlson and associates¹⁷). Thus if the tube is attached to an apparatus which keeps a persistent subatmospheric pressure, not only will coughing be rendered ineffective on that side, but matter in the bronchi will tend to be forced peripherally into the smaller respiratory passages, giving rise to collapse.

This subatmospheric pressure should not be increased to any great extent with the hope of completing the expansion of a partially collapsed lobe even many weeks after operation. A patient of mine responded well to this treatment and expansion appeared to be 80 per cent, when he suddenly collapsed and died in a few minutes. Postmortem examination showed that death was due to spontaneous pneumothorax of the opposite lung, on the anterior border of which were found numerous emphysematous bullae, though none were present on the side of operation. In this case the negative pressure had been gradually increased to 5 cm. of mercury in a period of about six weeks.

On return to the ward the patient is placed at once in Fowler's position. This, in spite of the spinal anesthesia, appears to be the most comfortable posture, and it also has the advantage of being the best both for drainage of the upper lobe bronchus and of the pleural cavity.

The oxygen tent is used for the first few days, more on account of the equitable temperature and freedom from draughts and air-borne infection which are possible with the modern thermostatically controlled machine than because of need of oxygen. In fact, oxygen should be used sparingly, as it increases the viscosity of the bronchial secretions, so making their elimination more difficult (Holinger¹⁸).

Coughing is encouraged, and it is not painful if manual support is given to the ribs. Breathing exercises, which have been learned before the operation, are commenced as soon as possible, with the object of increasing the respiratory movements of the affected side. Regular and systematic persuasion in coughing, expectoration and breathing exercises is most important, and opiates should be withheld until the patient has satisfactorily cleared his throat. Inhalations of 5 per cent carbon dioxide aid considerably. Should retention of secretions occur in spite of this, aspiration either by an intratracheal catheter or through the bronchoscope should be resorted to. In such cases chemotherapy with a sulfonamide compound is indicated, and it should also be employed and in large doses if pulmonary infection takes place, when the drug may be given by insufflation through the bronchoscope as well as by mouth. In some clinics bronchoscopic aspiration is carried out as a routine on completion of lobectomy; this may be of value when general anesthesia has been used, but I have never seen the need of it with a conscious patient operated on under spinal anesthesia. Neither have I found the bronchodilator effect of amyl nitrite (Nicholson¹⁹) of any obvious value in helping to get rid of secretions and to increase aeration of the lung; it has been tried in only 3 cases.

CONCLUSIONS

Bronchial obstruction and pulmonary infection and fibrosis are the important causes of collapse of the lung after lobectomy. Clinically they present as obstructive

16. Archibald, E., and Brown, A. L.: Cough: Its Action on Material in Tracheobronchial Tract; Experimental Study, *Arch. Surg.* **16**:322 (Jan) 1928.

17. Carlson, H. A.; Ballon, H. C.; Wilson, H. M., and Graham, E. A.: *J. Thoracic Surg.* **2**:573, 1933.

18. Holinger, P.; Basch, F. P., and Poncher, H. G.: Influence of Expectorants and Gases on Sputum and Mucous Membranes of Tracheobronchial Tree, *J. A. M. A.* **117**:675 (Aug. 30) 1941.

19. Nicholson, W. F.: *J. Thoracic Surg.* **9**:194, 1939.

massive collapse and as chronic progressive pneumonia with subsequent diffuse fibrosis.

The avoidance of pulmonary infection is the most important measure in the prevention of postlobectomy collapse.

Iodized oil appears to have no definite relation to postlobectomy collapse, save that it may give rise to lipid pneumonia.

Production of adhesions cannot be accurately controlled; even if successfully produced they cannot prevent the two common forms of collapse from occurring, and, finally, adhesions have been shown to cause postlobectomy collapse. For these reasons, their artificial production should be abandoned, and adhesions found at operation should be sectioned if they are likely to give rise to distortion of the remaining lung tissue.

The simplicity and the safety of spinal anesthesia with intratracheal oxygen are noted.

The importance of attaching the drainage tube to an apparatus which maintains a negative intrapleural pressure but allows coughing to take place against a positive pressure is stressed.

Prof. H. N. Green gave assistance in this study and allowed me to work in his department. Dr. H. E. Harding gave continual help; Prof. G. A. Clark allowed Mr. P. D. Greaves to do numerous estimations of the alkali reserve in his department; Dr. J. Rennie, medical officer of health, and Dr. J. Clark, medical superintendent, gave me permission to publish clinical cases.

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ROENTGENOLOGIC DEMONSTRATION OF SPINAL METASTASES FROM LEIOMYOSARCOMA OF THE UTERUS

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BOSTON

Leiomyosarcoma of the uterus is a relatively rare tumor, representing not more than 2 per cent of uterine leiomyomas.¹ [Miller and Rogers,² in a study made at the Massachusetts General Hospital covering fifty years (1876-1926), found an incidence of 1.4 per cent.] They also described a case in which metastasis to the hip

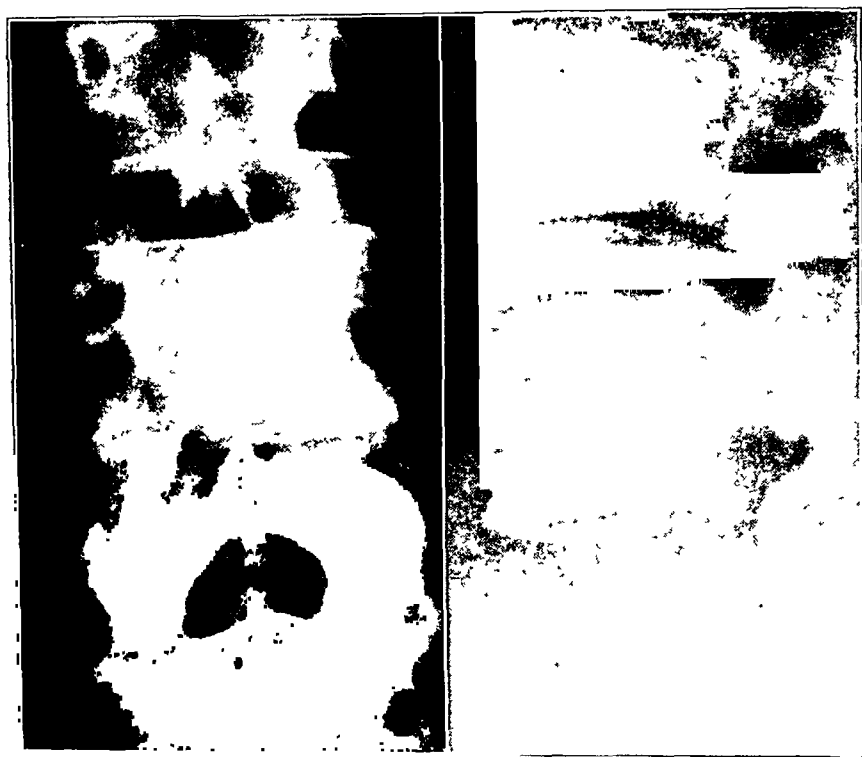


Fig. 1 (case 1).—Roentgenograms showing osteoblastic metastasis to the fourth lumbar vertebra approximately five years after hysterectomy. There is a certain similarity in appearance to the metastasis shown in figure 3, without quite as fine detail as is seen in the latter.

caused spontaneous fracture. Metastasis from leiomyosarcoma is even more rare than the primary tumor. Because the roentgenographic appearance of osteoblastic metastasis from leiomyosarcoma has received little if any emphasis in the published reports, 2 cases in which this diagnosis was proved are presented.

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¹ Whelock, M C, and Warren, S. Leiomyosarcoma of the Uterus, *Ann. Surg.* **116**: 882, 1942

² Miller, R H, and Rogers, H. Sarcoma of the Uterus, *New England J. Med* **198**: 927, 1928

REPORT OF CASES

CASE 1.—A 46 year old district nurse was first seen at the Massachusetts General Hospital in 1935 because of pain in the back and several palpable masses in the abdomen and

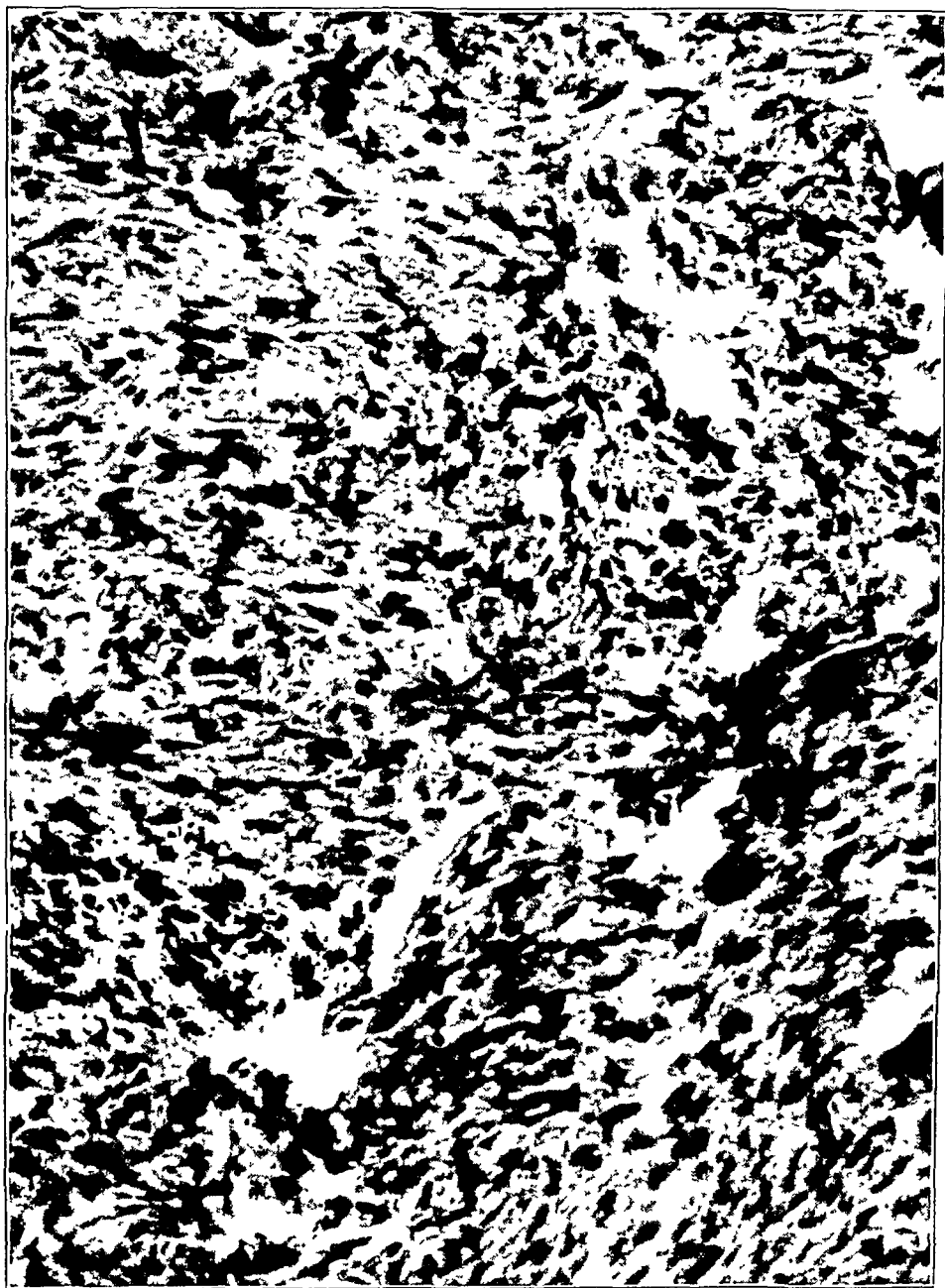


Fig. 2 (case 1).—Photomicrograph (section from fourth lumbar vertebra) showing leiomyosarcoma.

pelvis. Three years before, a total hysterectomy had been performed in another hospital, and an intramural leiomyosarcoma had been found. During the investigation of the cause of her pain, a roentgenogram of the abdomen revealed increased density of the fourth lumbar vertebra (fig. 1), as well as definite deformity of the psoas shadows

From 1935 to 1941 an extremely large amount of roentgen treatment was administered to various areas; on one occasion a radiation ulcer in the left upper quadrant of the abdomen was excised. The roentgenographic appearance of the fourth lumbar vertebra gradually changed, revealing progression of the destructive lesion, until by 1940 the vertebra had almost entirely collapsed. At this point a spinal fusion was done, and biopsy of material obtained from the fourth lumbar vertebra confirmed the diagnosis of metastatic leiomyosarcoma.

In December 1941 a cordotomy was performed for intractable pain; metastatic nodules in the chest were demonstrated by roentgenogram. The patient's final admission was in February 1942. She died the following April, slightly more than ten years after the original operation (hysterectomy) for leiomyosarcoma. Autopsy revealed metastatic leiomyosarcoma involving the liver, lungs and spine. The changes in the fourth lumbar vertebra were originally thought to represent osteoblastic metastasis, and in view of the history of removal of

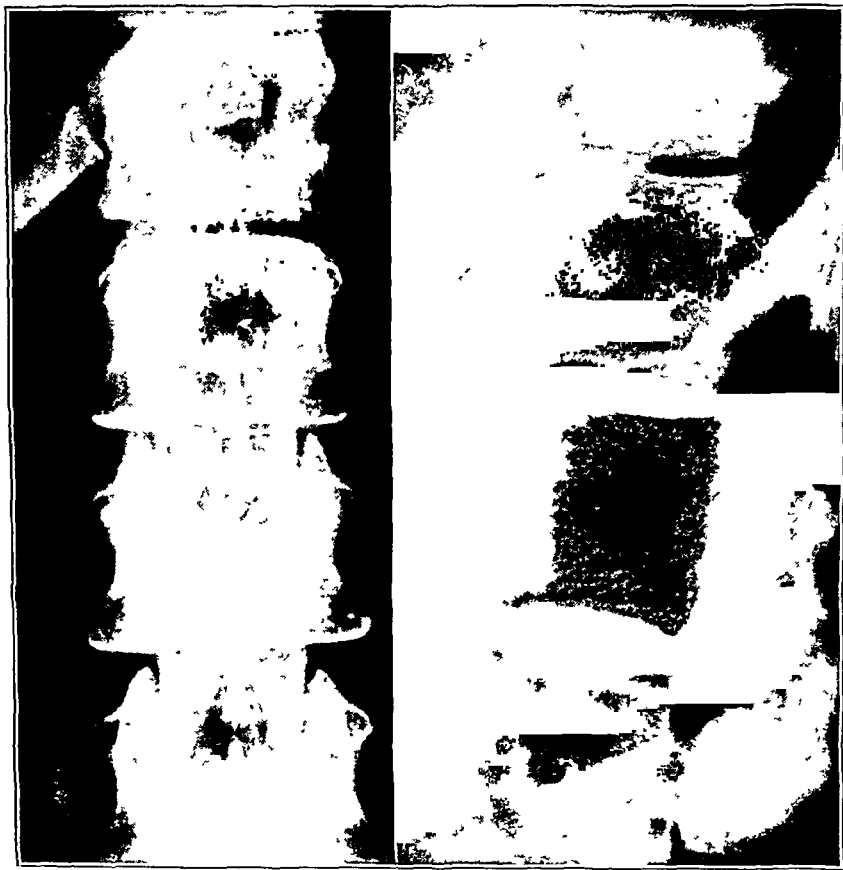


Fig 3 (case 2).—Localized roentgenograms of the second lumbar vertebra demonstrating the osteoblastic metastasis. Note the increased density of the second lumbar vertebra. Irregular lines of diminished density are seen in the pathologic area involving the posterior two thirds of the vertebra.

a leiomyosarcoma this tentative diagnosis was made; it was later confirmed histologically, both by biopsy and by necropsy (fig. 2).

Comment.—Inasmuch as the appearance of the bone is the point of importance in this report, the amount of roentgen therapy, the technic by which it was given and the various areas treated have not been described in detail. Although the various masses which were treated showed definite improvement under roentgen therapy, and this is remarkable considering the type of tumor involved, the bone lesion progressed slowly but steadily until the body of the fourth lumbar vertebra was almost completely destroyed.

The roentgenologic appearance of the metastatic involvement of the bone in case 1 led to the diagnosis in the following case.

CASE 2.—A 50 year old woman entered the Massachusetts General Hospital in June 1943 for study of pain in the lower part of the back, radiating down both legs. The pain was of

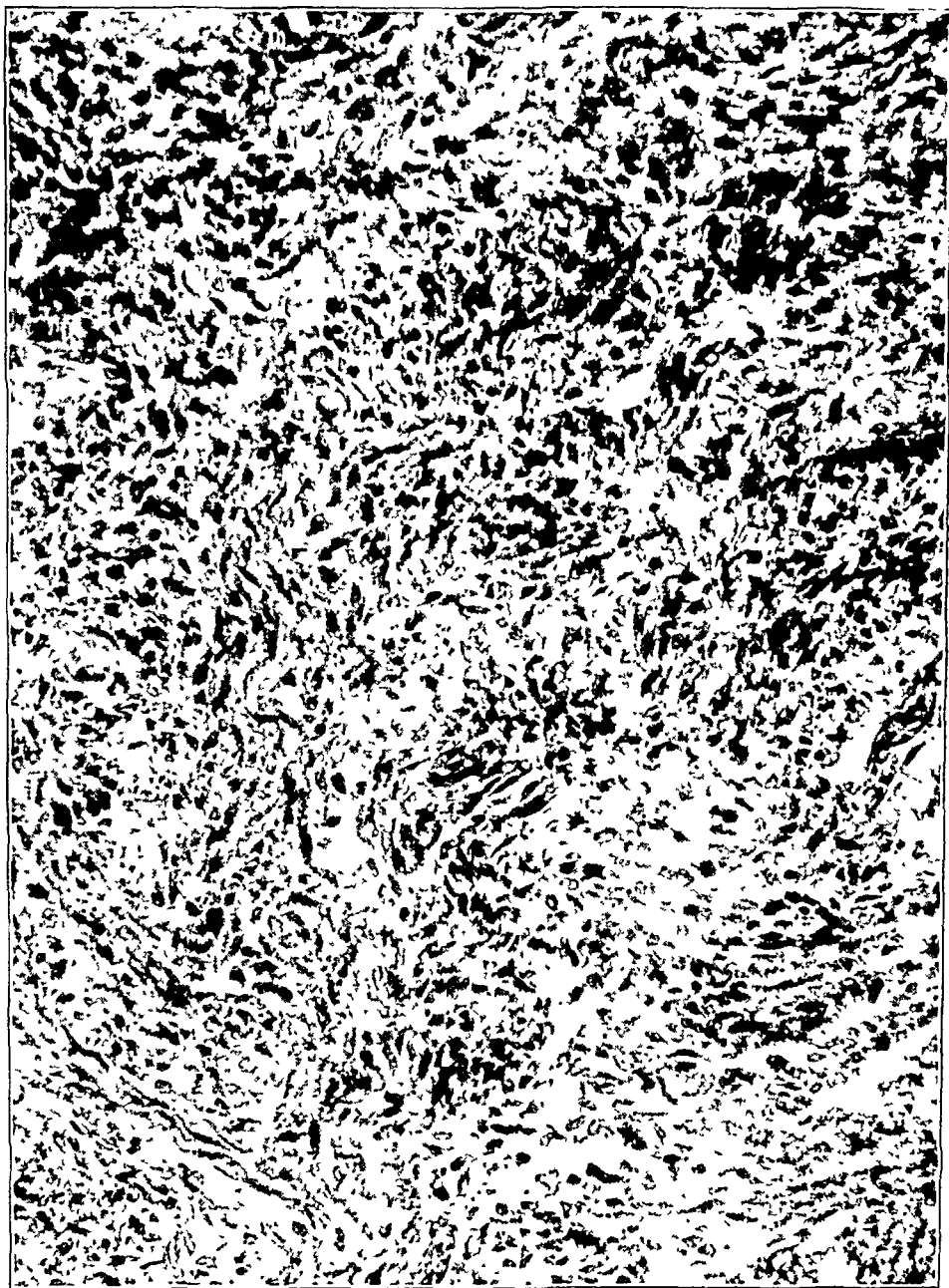


Fig. 4 (case 2).—Photomicrograph (section from tumor in the spinal canal overlying the second lumbar vertebra) showing leiomyosarcoma

one month's duration and had come on suddenly about forty-eight hours after the patient had jumped from a height of approximately 2 feet (60 cm). At another hospital, investigation of the cause of the pain revealed an abnormal second lumbar vertebra. The patient was given a small amount of roentgen treatment, which did not, however, relieve her pain.

The past history was noncontributory, except that an operation "for fibroids," at which part of the uterus and the left ovary and the left tube were removed, had been performed one year previous to her admission to this hospital.

The presence of a lesion in the second lumbar vertebra was established (fig. 3) and was interpreted as a sign of metastasis from a malignant tumor. An examination of the lumbar portion of the spinal canal with iodized poppyseed oil revealed a complete block just below the upper margin of the third lumbar vertebra. At operation a large mass of tumor was found protruding into the bony canal. Its main portion was over the body of the second lumbar vertebra, but it also extended above and below for a few centimeters. The histologic report was "metastatic leiomyosarcoma" (fig. 4).

Comment.—Although a specimen of bone could not be obtained for biopsy, it seems likely that the tumor in the spinal canal and that in the bone were of the same type because of their close proximity, and that they in all probability arose from the uterine tumor.¹

COMMENT

When the appearance of the roentgenograms of the vertebrae in the 2 cases is compared, a certain similarity is seen. In case 2, there is increased density surrounding irregular linear shadows which suggest the possibility of vascular channels, although this cannot be ascertained definitely. In case 1, it is seen that there is rather diffuse increased density but that there are poorly defined areas of rarefaction within this density. The linear shadows are not visualized as they are in case 2, but are suggested. Except for the irregular lines seen in the diseased areas there is no recognizable difference from any other form of osteoblastic metastasis. The roentgenograms in case 2 were taken with a rotating anode tube, and the peculiar pattern is particularly well demonstrated. It is possible that had the roentgenograms in case 1 been taken with a tube of corresponding focal spot they might have shown more resemblance to this appearance.

It is not believed that the present status of roentgenology allows a definite etiologic differentiation of osteoblastic metastasis. However, the peculiar pattern shown in case 2 has not been previously described or recognized so far as can be determined. The diagnosis may be suspected when there is a history of hysterectomy or of preceding leiomyosarcoma of the uterus, and if roentgenologic study reveals a focus of metastatic malignant growth. It is understood that osteoblastic metastases may be produced by other malignant uterine tumors.

There was osteoblastic metastasis in both of the 2 cases presented. This type of metastasis, in contradistinction to the osteolytic form, may possibly be explained on the basis of the relatively slow growth of the tumor. It may spread by way of the vertebral veins,³ as carcinoma of the prostate so commonly does.

SUMMARY

Attention is called to the fact that osteoblastic metastasis may be produced by leiomyosarcoma of the uterus.

Two cases in which there was proved metastasis from leiomyosarcoma of the uterus to the lumbar portion of the spine are reported, and their roentgenologic appearance is described.

These cases are published with the permission of Drs. W. J. Mixter and C. G. Mixter.

The Massachusetts General Hospital.

3. Batson, O. V.: The Function of the Vertebral Veins and Their Role in the Spread of Metastasis, *Ann. Surg.* **112**:138, 1940.

GERMICIDAL ACTIVITY OF ALCOHOL, HYDROCHLORIC ACID AND ALUMINUM POTASSIUM SULFATE

THEIR EFFECT ON CUTANEOUS FLORA

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It is generally thought that the skin is able in some manner to destroy bacterial organisms with which it comes in contact. This ability has been referred to as the "self-disinfecting power of the skin" by Arnold and his co-workers¹ (1930).

Colebrook² (1930) observed the disappearance of exogenous bacteria from the surface of normal skin and suggested that it may be due to (1) desiccation, (2) activity of a lysozyme or (3) concentration of salts of sweat. He believed that neither desiccation nor lysozyme is an important factor but that concentration of salts of sweat may be a factor. Bryan and Mallmann³ (1933) expressed the opinion that desiccation plays an important role, as did also Norton and Novy⁴ (1931). Meleney⁵ (1927) stated that the bactericidal action of sweat and of sebaceous glands is of relatively little importance. Usher⁶ (1928) showed that sweat is a good culture medium.

Arnold (1930) and Sharlit and Scheer⁷ (1923) found the superficial layers of the skin to be acid and to have a p_H of 5 to 5.7. Marchionini and Hausknecht,⁸ Marchionini, Schmidt and Kiefer⁹ (1938) and Marchionini and Schmidt¹⁰ (1939)

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1. Arnold, L.; Gustafson, C. J.; Hull, T. G.; Montgomery, B. E., and Singer, C.: The Self-Disinfecting Power of the Skin as a Defense Against Microbic Invasion, *Am. J. Hyg.* **11**:345, 1930.

2. Colebrook, L.: Memorandum on the Sterilization of the Hands, in Interim Report of Departmental Committee on Maternal Mortality and Morbidity, Ministry of Health, London, His Majesty's Stationery Office, 1930, pp. 122-135.

3. Bryan, C. S., and Mallmann, W. L.: Some Factors Responsible for the So-Called Self-Disinfecting Power of the Skin, *J. Lab. & Clin. Med.* **18**:1249, 1933.

4. Norton, J. F., and Novy, M.: Studies on the Self-Disinfecting Power of the Skin, *Am. J. Pub. Health* **21**:1117, 1931.

5. Meleney, F. L.: Bacteriologic and Immunologic Aspects of Surgery, in Nelson Loose-Leaf Surgery, New York, Thos. Nelson & Sons, 1927, vol. 1, p. 83.

6. Usher, B.: Human Sweat as a Culture Medium for Bacteria, *Arch. Dermat. & Syph.* **18**:276 (Aug.) 1928.

7. Sharlit, H., and Scheer, M.: The Hydrogen-Ion Concentration of the Surface of the Healthy Intact Skin, *Arch. Dermat. & Syph.* **7**:592 (May) 1923.

8. Marchionini, A., and Hausknecht, W.: Säuremantel der Haut und Bakterienabwehr: Die regionäre Verschiedenheit der Wasserstoffionenkonzentration der Hautoberfläche, *Klin. Wchnschr.* **17**:663, 1938.

9. Marchionini, A.; Schmidt, R., and Kiefer, J.: Säuremantel der Haut und Bakterienabwehr: Ueber die regionäre Verschiedenheit der Bakterienabwehr und Desinfektionskraft der Hautoberfläche, *Klin. Wchnschr.* **17**:736, 1938.

10. Marchionini, A., and Schmidt, R.: Säuremantel der Haut und Bakterienabwehr: Der Bakteriengehalt in pathologischen Lücken des Säuremantels, *Klin. Wchnschr.* **18**:461, 1939.

reported on the acid-base conditions of the skin. They pointed out that diseased areas show a higher bacterial count and are more alkaline than normal areas. They have also shown that the cutaneous surface is acid if sweat is allowed to evaporate, but if this is prevented the ammoniacal products which are formed cause an alkaline reaction. Pillsbury and Shaffer¹¹ (1939) also tested the p_H of the skin and made similar observations.

Bernstein and Hermann¹² (1942) found that the p_H of the hands was 3.5 to 5.8, of the groins 5.5 to 6.3, of the areas between the toes 5.5 to 6.5 and of the armpits 6.5 to 8.0. They reported an increase in acidity when the temperature was high, indicated by a decrease in the p_H from 5.8 to 4.0.

Davletov¹³ (1940) published an article in Russian which later was translated into English and published in the *Bulletin of War Medicine* (1942). In it are reported his observations on the effect of acid on the bacterial flora of the skin. He found that a 0.1 per cent solution of hydrochloric acid is an effective disinfecting agent for surgeons' hands and that the bactericidal power is further enhanced by the addition of 20 per cent to 40 per cent of "surgical spirit."

The methods for obtaining material for study of the bacterial flora of the skin and the effect of germicidal agents on it have mostly consisted of swabbing, scraping and cutting sections of skin for culture and impression. It is difficult to secure quantitative results with any of these methods.

Price¹⁴ in 1938 published a new quantitative method of studying the bacterial flora of the skin, which consisted of scrubbing the hands and arms with brush, soap and water in fourteen consecutive basins. Later Price¹⁵ (1939) adapted this method to the study of the effectiveness of ethyl alcohol, mercury bichloride, potassium iodide and Harrington's solution for the disinfection of the skin. He concluded that when properly used a solution containing exactly 70 per cent by weight of ethyl alcohol is the most effective of all for preoperative preparation of the hands and arms.

Pohle and Stuart¹⁶ (1940, 1941) used a modification of the Price technic in the study of cleaning agents, rosin and fatty acid rosin soaps.

Cromwell and Leffler¹⁷ (1942) reported experiments using Pohle and Stuart's modification. They found that aluminum and potassium sulfate in 10 per cent aqueous solution, though not germicidal, gives as good a "bacterial destruction curve" as a 70 per cent solution of alcohol.

11. Pillsbury, D. M., and Shaffer, B.: Cutaneous Reaction with Reference to the Surface p_H , the Reaction to Ointments and Solutions of Different p_H and the Effect of the Skin in Modifying the p_H of Applied Solutions, *Arch. Dermat. & Syph.* **39**:253 (Feb.) 1939.

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14. Price, P. B.: The Bacteriology of Normal Skin: A New Quantitative Test Applied to a Study of the Bacterial Flora and the Disinfectant Action of Mechanical Cleansing, *J. Infect. Dis.* **63**:301, 1938.

15. Price, P. B.: Ethyl Alcohol as a Germicide, *Arch. Surg.* **38**:528 (March) 1939; Mercuric Chloride, Potassium Mercuric Iodide and Harrington's Solution in Skin Disinfection, *Surg., Gynec. & Obst.* **69**:594, 1939.

16. Pohle, W. D., and Stuart, L. S.: (a) The Germicidal Action of Cleaning Agents: A Study of a Modification of Price's Procedure, *J. Infect. Dis.* **67**:275, 1940; (b) The Germicidal Activity of Rosin Soap and Fatty Acid Rosin Soap as Indicated by Hand Washing Experiments, *Oil & Soap* **18**:2, 1941.

17. Cromwell, H. W., and Leffler, R.: Evaluation of "Skin Degerming" Agents by a Modification of the Price Method, *J. Bact.* **43**:51, 1942.

Kronig and Paul¹⁸ (1897) first showed that the germicidal efficiency of acids is proportional to the hydrogen ion concentration of their solutions. Winslow and Lochridge¹⁹ (1906) showed that a 0.0077 normal solution of hydrochloric acid will produce a 99 per cent reduction in the number of *Escherichia coli* in forty minutes.

Beyer²⁰ (1911) and Gregersen²¹ (1916) compared solutions containing exactly 70 per cent of alcohol by weight with solutions containing 70 per cent by volume. Both workers concluded that the solution containing 70 per cent by weight is superior as a germicide in vitro. Price¹⁵ (1939) reported that in using his method 70 per cent by weight proved to be the most efficient concentration of alcohol. Pohle and Stuart^{16a} (1940) also found this solution to be an efficient agent when the technic of Price was used.

Alum has always been regarded as a powerful astringent, and its most important use today is as a local astringent. There are few references to its antiseptic properties. According to Miquel,²² it will inhibit the multiplication of bacteria in the proportion of about 1 part in 200.

It may be assumed from the literature cited that a low p_H is a factor in the self-disinfecting power of the skin. It is also known that hydrochloric acid is an efficient germicide in vivo and in vitro. Cognizant of the existence of these two factors, we decided to apply the technic outlined by Price, to evaluate quantitatively the effect of a 0.5 per cent solution of hydrochloric acid on the bacterial flora of the hands and arms and to compare it with the effect of a solution containing 70 per cent of alcohol by volume and that of a 10 per cent solution of aluminum and potassium sulfate. We also wished to estimate the bacterial flora of the hands and arms after the wearing of rubber gloves.

METHOD

The basins were wrapped in paper and sterilized in the autoclave. Fourteen were generally used in each experiment. One thousand to 1,500 cc. of distilled water was placed in each basin. Surgeons' scrub brushes were wrapped and sterilized in the autoclave. A white toilet soap was used throughout the experiments. Surgeons' rubber gloves were powdered, wrapped in a towel and sterilized in the autoclave.

One minute was used as the period of washing at each bowl. Exactly ten seconds was allowed for soaping the brushes, hands and arms; then the hands and arms were scrubbed for thirty-five seconds. The brush was then dropped into the basin, and the soap was rinsed off the hands and arms for fifteen seconds. This same procedure was repeated at each wash basin. In experiments in which test solutions were used, they were applied after seven minutes of scrubbing with soap and water. A piece of sterile gauze was used, and the hands and arms were sponged for two minutes. Then scrubbing was again resumed for a period of seven minutes.

One cubic centimeter of wash water from each basin was placed in a sterile Petri dish, and liquefied agar was poured in, thoroughly mixed with the sample and allowed to harden. Plates were incubated for forty-eight hours at 37 C. The bacteria were then counted and

18. Kronig, B., and Paul, T.: *Die chemischen Grundlagen der Lehre von der Giftwirkung und Desinfection*, Ztschr. f. Hyg. **25**:1, 1897.

19. Winslow, C.-E. A., and Lochridge, E. E.: *The Toxic Effect of Certain Acids upon Typhoid and Colon Bacilli in Relation to the Degree of Their Dissociation*, J. Infect. Dis. **3**:547, 1906.

20. Beyer, A.: *In welcher Konzentration tötet wässriger Alkohol allein, oder in Verbindung mit anderen desinfizierenden Mitteln Entzündungs- und Eiterungserreger am schnellsten ab?* Ztschr. f. Hyg. u. Infektionskr. **70**:225, 1911.

21. Gregersen, J. P.: *Untersuchungen über die desinfizierende Kraft der desinfizierenden Stoffe in Verhältnis zu ihrer Konzentration*, Zentralbl. f. Bakt. (Abt. 1) **77**:168, 1916.

22. Miquel, in Wood, H. C., and others: *The Dispensatory of the United States of America*, ed. 22, Philadelphia, J. B. Lippincott Company, 1937.

the totals calculated. In preparing the curves we used the method of Pohle and Stuart; that is, the bacterial count per basin was plotted as the abscissa and the basin number as the ordinate.

Sterile rubber gloves were used in a series of experiments and were worn for one hour. They were put on the hands after the application of the test solution and subsequent drying with a sterile towel. A solution containing 70 per cent of alcohol by volume, a 0.5 per cent solution of hydrochloric acid (0.137 normal) and a 10 per cent solution of aluminum and potassium sulfate were the test solutions used in these experiments.

RESULTS

The results given in the following tables are averages of from four to eight individual tests. Curves were plotted from these results.

TABLE 1.—*Normal Procedure*

Experiments	Bacterial Counts per Basin in Thousands													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Soap and water scrubbing.....	4,580	4,675	4,164	3,355	3,270	2,658	2,257	2,320	1,547	1,738	1,563	1,137	1,053	821
2. Distilled water scrubbing*.....	3,674	4,194	2,445	2,372	2,090	1,796	1,622	1,260	1,224	1,350	948

* Eleven basins were used in this series.

1. Results plotted in chart 1.

2. Results plotted in chart 2.

TABLE 2.—*Test Solutions*

Experiments (Soap and Water in All Basins)	Bacterial Counts per Basin in Thousands														
	1	2	3	4	5	6	7		8	9	10	11	12	13	14
3	4,054	3,740	3,221	2,940	2,636	1,898	1,560	Hydrochloric acid, 0.5%: 2 min. *0	23	29	38	38	49	51	62
4	3,608	4,084	3,359	1,859	2,034	1,592	1,433	Alcohol, 70% by vol.: 2 min. *0	0	12	15	18	16	10	12
5	9,600	6,210	5,640	3,990	3,180	2,940	1,628	Potassium alum, 10%: 2 min. *448	358	224	315	289	330	357	310

* Bacterial count per cubic centimeter of test solution.

3. Results plotted in chart 3.

4. Results plotted in chart 4.

5. Results plotted in chart 5.

TABLE 3.—*Test Solutions Plus the Wearing of Rubber Gloves*

Experiments (Soap and Water in All Basins)	Bacterial Counts per Basin in Thousands														
	1	2	3	4	5	6	7		8	9	10	11	12	13	14
6	7,787	5,422	4,610	2,810	2,767	2,542	2,267	Gloves worn for 1 hour	2,842	2,520	2,475	2,222	2,047	2,092	1,350
7	5,788	5,512	4,918	3,609	3,250	2,233	2,178	Hydrochloric acid, 0.5%: 2 min.; gloves 1 hour *0	403	501	469	495	438	463	433
8	6,062	5,008	3,636	4,075	3,310	3,287	2,709	Alcohol, 70% by vol.: 2 min.; gloves 1 hour *0	21	27	29	22	28	20	23
9	7,650	7,830	7,695	5,085	4,860	3,820	3,105	Potassium alum, 10%: 2 min.; gloves 1 hour *930	1,845	2,280	2,025	2,835	1,890	2,395	2,385

* Bacterial count per cubic centimeter of test solution

6. Results plotted in chart 6.

7. Results plotted in chart 7.

8. Results plotted in chart 8.

9. Results plotted in chart 9.

COMMENT

We found that the numbers of organisms removed from the hands and arms in the soap and water series and the distilled water series were reasonably similar. From the curve shown in chart 2 it appears that the first period of scrubbing is required to loosen the epithelium and remove fat. Maximum removal of bacteria is delayed until the second period. This delay is not as apparent for the scrubbing with soap and water (chart 1). There is also a much more gradual decrease after the second basin in the distilled water series. This observation differs from those of Price, who found that brushing the skin without soap reduces the basic flora more rapidly than does the use of soap.

In the group of hand washing experiments in which test solutions were used, we found alcohol in a concentration of 70 per cent by volume to be a highly efficient germicidal agent for the flora of the skin. The removal curve in chart 4 illustrates the effect.

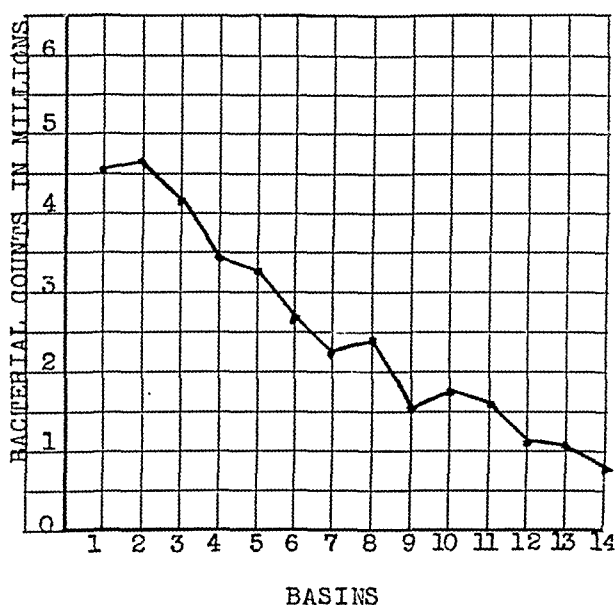


Chart 1.—Removal curve of scrubbing with soap and water.

A 0.5 per cent solution of hydrochloric acid was also found to be a highly efficient germicidal solution. Davletov¹³ found that a 0.1 per cent solution was an efficient disinfecting agent for the skin, but we obtained more favorable results with a 0.5 per cent solution. The solution was not irritating to the skin of any volunteer. In fact, the skin was extremely soft and smooth during the time this solution was being used in our experiments. The removal curve in chart 3 shows 0.5 per cent hydrochloric acid to be an efficient germicidal agent for the resident flora of the skin.

A 10 per cent solution of aluminum and potassium sulfate proved rather efficient in reducing the bacterial flora of the skin but was not as effective as alcohol or hydrochloric acid. We agree with Cromwell and Leffler¹⁷ that it does give a good "bacterial destruction curve," as is apparent in chart 5.

In the series of experiments in which rubber gloves were used, the first group served as the control. The subjects scrubbed the hands with soap and water in seven basins, wore rubber gloves for one hour and then scrubbed in seven additional

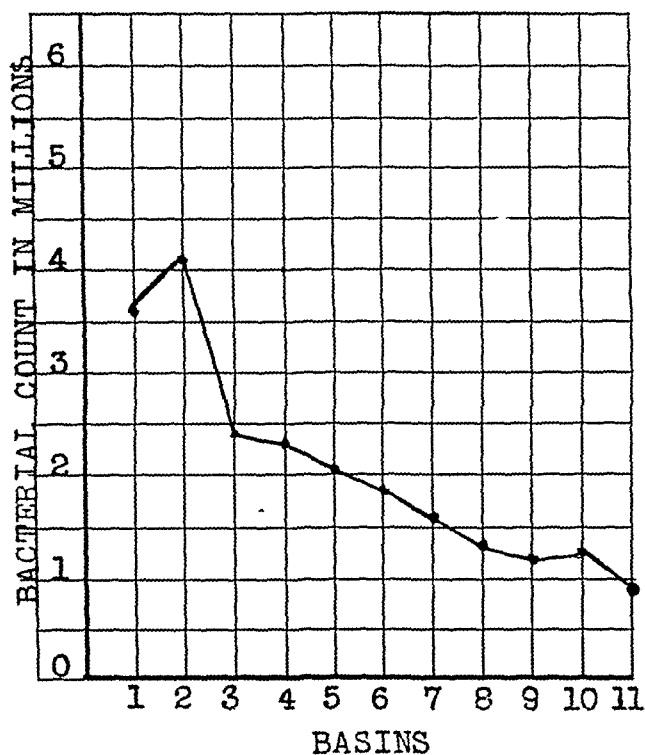


Chart 2.—Removal curve of scrubbing with distilled water.

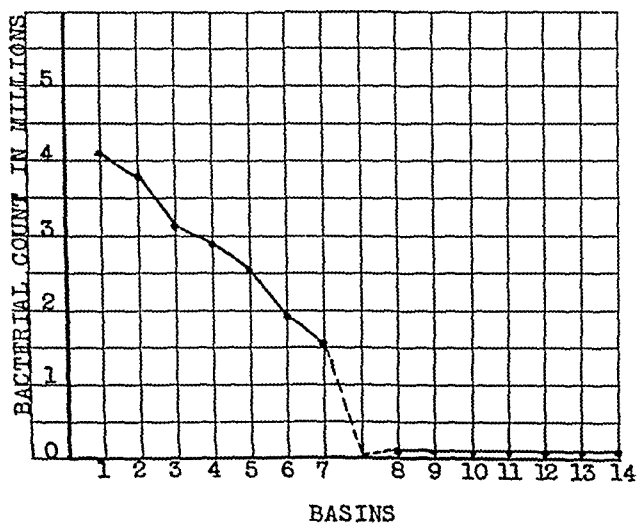


Chart 3.—Removal curve of a procedure which included scrubbing with soap and water in the first seven basins, application of a 0.5 per cent solution of hydrochloric acid for two minutes and scrubbing with soap and water in the last seven basins.

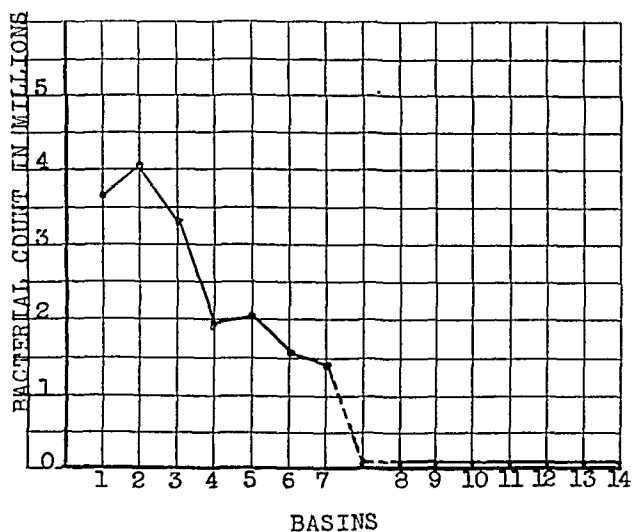


Chart 4.—Removal curve of a procedure which included scrubbing with soap and water in the first seven basins, application of a solution containing 70 per cent of alcohol by volume for two minutes and scrubbing with soap and water in the last seven basins.

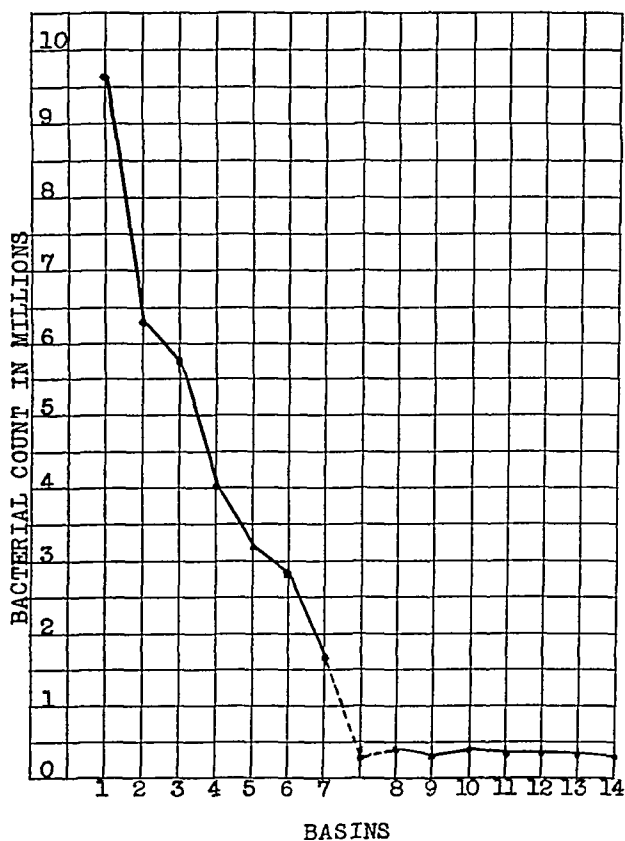


Chart 5.—Removal curve of a procedure which included scrubbing with soap and water in the first seven basins, application of a 10 per cent solution of aluminum and potassium sulfate for two minutes and scrubbing with soap and water in the last seven basins.

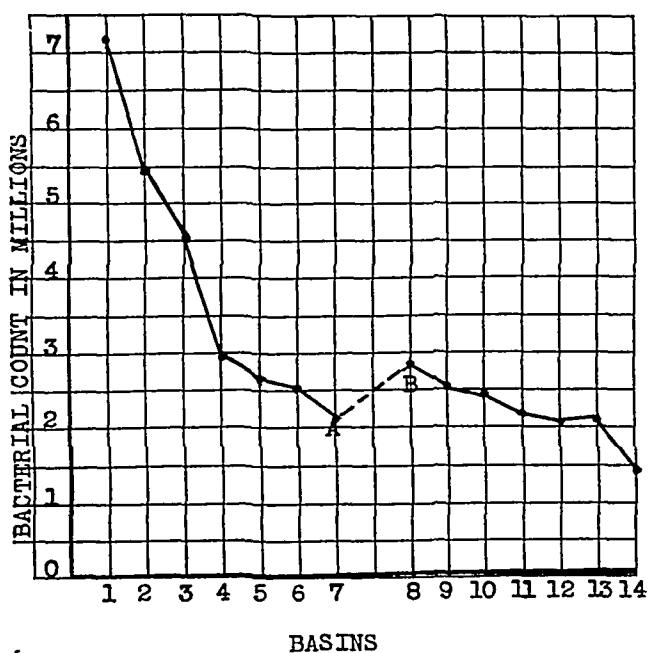


Chart 6—Removal curve of a procedure which included scrubbing with soap and water in the first seven basins, wearing sterile rubber gloves for one hour and scrubbing with soap and water in the last seven basins. The dotted line A-B represents the interval during which rubber gloves were worn.

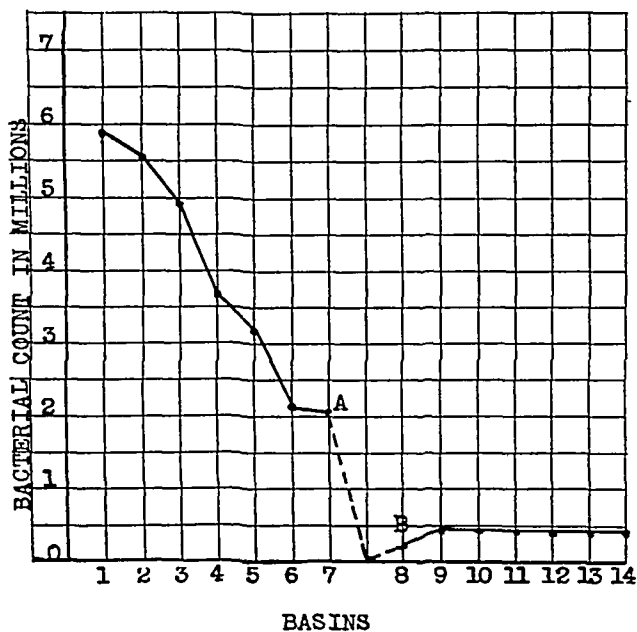


Chart 7—Removal curve of a procedure which included scrubbing with soap and water in the first seven basins, application of a 0.5 per cent solution of hydrochloric acid for two minutes, wearing sterile rubber gloves for one hour and scrubbing with soap and water in the last seven basins. The dotted line A-B represents the interval during which rubber gloves were worn.

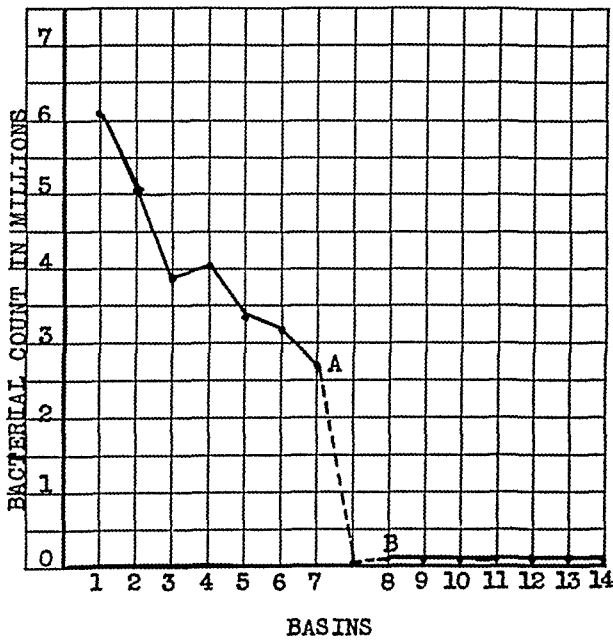


Chart 8.—Removal curve of a procedure which included scrubbing with soap and water in the first seven basins, application of a solution containing 70 per cent of alcohol by volume for two minutes, wearing sterile rubber gloves for one hour and scrubbing with soap and water in the last seven basins. The dotted line *A-B* represents the interval during which rubber gloves were worn.

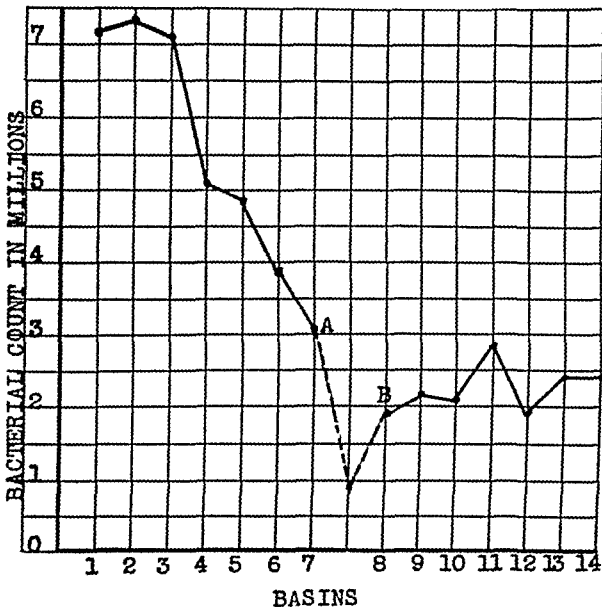


Chart 9.—Removal curve of a procedure which included scrubbing with soap and water in the first seven basins, application of a 10 per cent solution of aluminum and potassium sulfate for two minutes, wearing sterile rubber gloves for one hour and scrubbing with soap and water in the last seven basins. The dotted line *A-B* represents the interval during which rubber gloves were worn.

basins. The results of these experiments are given in table 3. We found that after rubber gloves had been worn for one hour the bacteria were more numerous than after the regular scrubbing with soap and water. By comparing chart 1 with chart 6 one may readily observe this effect.

When a 70 per cent solution of alcohol was used prior to the wearing of the rubber gloves, the bacterial counts rose only slightly, as is seen in table 3 and in the curve in chart 8.

When a 0.5 per cent solution of hydrochloric acid was used prior to the wearing of the rubber gloves, the bacterial counts rose somewhat higher than those in the alcohol series. However, it still was efficient when compared with the soap and water used in the control experiments. The results are plotted in chart 7.

When a 10 per cent solution of aluminum and potassium sulfate was used prior to the wearing of the rubber gloves, the bacterial counts rose and were much like those of the control, except that as the astringent action was overcome by the scrubbing, the counts became higher, as indicated in the ninth to the fourteenth basin. The results are plotted in chart 9.

CONCLUSIONS

Alcohol in a concentration of 70 per cent by volume was found to be an efficient germicidal agent for the bacterial flora of the skin when used as outlined in these experiments.

A 0.5 per cent solution of hydrochloric acid was found to be highly efficient also but not entirely comparable to the alcohol.

Aluminum and potassium sulfate in 10 per cent aqueous solution evidently hardens the skin to such an extent that the organisms are imprisoned but not killed. They may be released after the softening of the skin which occurs when rubber gloves are worn and then removed in the subsequent scrubbing.

We believe that either alcohol 70 per cent by volume or hydrochloric acid 0.5 per cent is sufficiently efficient to use in the presurgical preparation of the surgeon's hands and that a 0.5 per cent solution of hydrochloric acid could safely be used so as to conserve the supply of alcohol for more essential purposes.

We believe that a 0.5 per cent solution of hydrochloric acid has a true germicidal action on the bacterial flora of the skin.

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PRIMARY TUBERCULOSIS OF THE SPLEEN

REPORT OF A CASE

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AND

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Hepatosplenomegaly is a very significant finding in an abdominal examination and often leads to a study of the entire gamut of differential diagnoses. The more common causes of this interesting change are sufficiently well catalogued to show tuberculosis as an infrequent offender. However, because of its obscurity and its amenability to treatment, tuberculosis of the spleen forms a worthy chapter in the study of the surgical splenopathies.

Intelligent understanding of this disease dates back to Winternitz'¹ work. According to Winternitz, and this has been substantiated by most subsequent writers, tuberculosis of the spleen is not a primary disease in the strict pathologic sense. Evidence of earlier tuberculous infection was found in all his autopsies. However, as a clinical entity the disease may be considered primary. In the spleen, tuberculosis may form an active focus for systemic infection. In this respect splenic tuberculosis is analogous to renal tuberculosis, which is secondary to some healed or inactive focus elsewhere but may act independently as a nidus of infection. The factors which determine the pathologic patterns in splenic tuberculosis are:¹ (1) the general reaction of the spleen to acute infection, manifested as hypertrophy and engorgement, (2) the specific lesions due to the tubercle bacilli and their localization and (3) the reparative process of the tissue after injury.

In the acute form of the disease, hypertrophy and engorgement are most pronounced, and the specific lesion may be slight if the course is rapid. Generally the specific lesion is more evident.

In the chronic productive form, fibrosis will predominate over splenic hypertrophy and tubercle formation. The common picture is that of a healing process vying with tuberculous activity, the result being a huge spleen which shows sclero-caseous changes.

Clinically three types of disease can be recognized.² In the acute type the infection is overwhelming and the spleen is enlarged and soft, with an engorged pulp. In the subacute form the spleen is larger and firmer, with pronounced tuberculous nodules. In the chronic form the spleen is very large and may be calcified; there are adhesions to the surrounding viscera. The incidence of the disease is greatest between 20 and 40 years of age. The acute type is characterized by high fever, profuse sweats and acute splenic tumor. In the chronic disease there are pain in the left upper quadrant of the abdomen, gastrointestinal disturbances, anorexia, lassitude, anemia, loss of weight and fever. On physical examination the spleen is always enlarged and may be nodular and hard. The liver and super-

This paper is published with the approval of the Veterans Administration, which, however, does not assume responsibility for the opinions expressed or the conclusions drawn by the authors.

1. Winternitz, M. C.: Tuberculosis of Spleen, *Arch. Int. Med.* **9**:680-697 (June) 1912.

2. Frank, T. J.: Primary Tuberculosis of Spleen, *Roy. Melbourne Hosp. Clin. Rep.* **10**: 113-118, 1939.

ficial lymph nodes may be enlarged. Winternitz¹ observed hepatic involvement in 80 per cent of the cases in which the liver was examined. Involvement of lymph nodes was present in 57 per cent of his cases. There may be tuberculous involvement in other parts of the body. In the same series 40 per cent of the patients showed evidence of pulmonary tuberculous disease. In 16 per cent the lesions were healed, and in 24 per cent they were active. The laboratory examinations should include a complete study of the blood, roentgenograms of the chest and the abdomen and biopsy of enlarged lymph nodes. The results of studies of the blood are non-specific. Polycythemia, thrombopenic purpura, hemolytic anemia and Banti's anemia have been described.² Weiner and Carter³ reported a case of acute thrombopenic purpura with miliary tuberculosis of the spleen in which recovery followed splenectomy.

The treatment of this disease is splenectomy. An enlarged liver and involved lymph nodes or inactive peritoneal tuberculosis are no contraindication, according to Frank.² Hickling⁴ reported 2 cases in which there was roentgen evidence of miliary tuberculosis. The patients recovered, and the signs of involvement of the chest disappeared after splenectomy. Solomon and Doran⁵ report a case in which the patient showed involvement of the liver and the inguinal lymph nodes but recovered after splenectomy.

The rationale of splenectomy, then, is to remove an active focus of tuberculous infection and prevent further hematogenous spread. While the literature contains reports of cures in the presence of extrasplenic tuberculosis, our attitude is not so sanguine. We do feel, however, that considerable benefit can be derived from splenectomy and that the indications should merely postulate a spleen that can be demonstrated as the seat of active disease.

We wish to add our experience in the diagnosis and treatment of a case of splenic tuberculosis.

REPORT OF CASE

It was difficult to secure a good history from this patient, a Negro 47 years of age. He was admitted to the Veterans Hospital Dec. 15, 1941, complaining of vertigo and weakness. He also had dyspnea and cough. While at home the patient had complained of sweats and fever and had lost 20 pounds (9 Kg.) in weight. His appetite was poor, and he had occasionally observed blood in his stools. He said he had not had syphilis, gonorrhea or malaria. The duration of symptoms could not be determined.

On examination the patient appeared to be poorly nourished and chronically ill but fairly well developed. Examination of the neck revealed several hard, fixed, matted supraclavicular lymph nodes on the left side. The chest was resonant throughout. The breath sounds were normal, no rales were heard and there was normal fremitus. Examination of the heart showed the point of maximum intensity to be in the fifth interspace in the midclavicular line. The sounds were of good quality. Numerous extrasystoles were present, and the rate was rapid. Blood pressure was 130 systolic and 70 diastolic. The radial arteries were thickened. The edge of the liver could be felt four fingerbreadths below the right costal margin. It was firm and smooth. The spleen was decidedly enlarged, extending down to the iliac crest, and it was hard and nodular. A reducible hernia in the right inguinal region was present.

A blood count at the time of the patient's admission to the hospital showed 1,600,000 red cells and a hemoglobin content of 34 per cent. The total number of white cells was 12,200, with 64 per cent polymorphonuclears. There were 58 segmented cells, 6 stab cells, 31 lymphocytes, 3 monocytes, 1 eosinophil and 1 basophil. The sedimentation rate was 135.

3. Weiner, J. J., and Carter, R. F.: Acute Thrombocytopenic Purpura Hemorrhagica Associated with Miliary Tuberculosis of Spleen: Recovery with Splenectomy, *Ann. Surg.* **113**:57-61, 1941.

4. Hickling, R. A.: Tuberculous Splenomegaly with Miliary Tuberculosis of Lungs, *Quart. J. Med.* **7**:263-269, 1938.

5. Solomon, H. A., and Doran, W. T., Jr.: Primary Tuberculosis of Spleen, *New York State J. Med.* **39**:1288-1295, 1939.

The stools were found to contain occult blood. The icterus index was 5. *Plasmodium malariae* could not be found in the blood. Urinalyses gave essentially normal results. Agglutination tests for typhoid, paratyphoid, typhus and undulant fever gave negative results. Cultures of the stools for typhoid, paratyphoid and dysentery were negative.

Retrograde urography was performed to determine whether the mass in the left upper quadrant of the abdomen was an enlarged kidney. Pyelograms showed evidence of distortion and displacement of the left kidney due to extrinsic pressure. A specimen of the patient's urine was injected into a guinea pig, but tuberculosis was not found at autopsy of the animal. The initial roentgenogram of the chest appeared normal.

While in the hospital the patient exhibited a hectic febrile course. He complained of lack of appetite and of weakness. In view of the cervical lymphadenopathy, the hepatosplenomegaly and the febrile course, a presumptive diagnosis of tuberculosis of the spleen was made. On Jan. 16, 1942, a supraclavicular lymph node on the left side was excised. It

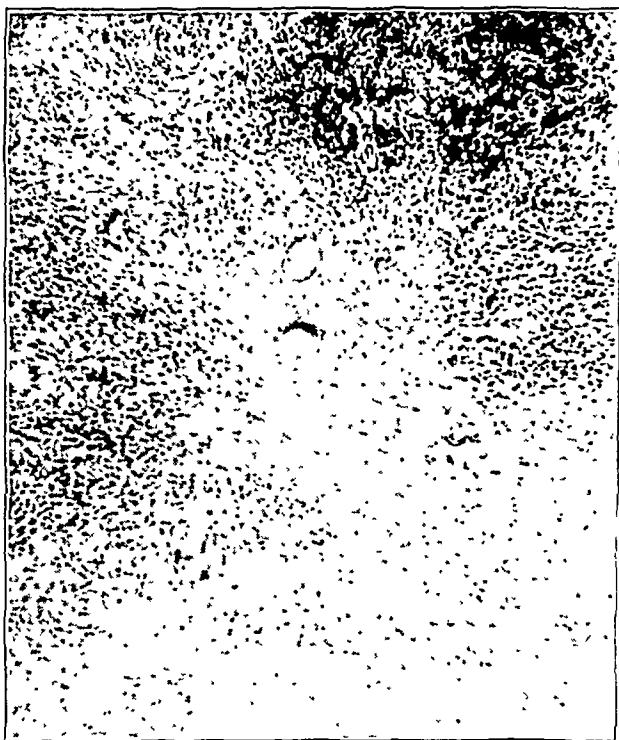


Fig. 1.—Microscopic section showing tuberculosis of a lymph node from the left supraclavicular region. Giant cells are clearly seen.

was found to be tuberculous. This strengthened the presumption of tuberculosis of the spleen. The report of the pathologist, Dr. Henry S. Blank, was as follows:

Gross Appearance.—The specimen consisted of a lymph node about the size of a small hickory nut. It measured 3 by 2.5 by 1.8 cm. The organ appeared to have been removed intact. The capsule was smooth and presented a slight degree of cyanosis. On section the node manifested increased resistance. The cut surface was pinkish white, with a slight yellowish mottling which suggested infiltration by a malignant or tuberculous process.

Microscopic Appearance.—The section was that of a lymph node presenting considerable distortion of the normal architectural pattern. The capsule was fairly well preserved. The remainder of the node had been completely destroyed by a necrotic and fibrotic process. In several areas the focal necrosis was characteristic of tuberculosis, and occasionally typical tubercle formation was observed. Numerous Langhans giant cells were seen. Except at isolated points just under the capsule, where a diffuse sprinkling of lymph, monocytoïd and plasma cells was noted, the remainder of the section was acellular. A diagnosis of tuberculosis was made.

The patient was given a transfusion of 500 cc. of whole blood on January 24, January 30 and February 6. The hemoglobin content of his blood rose to 59.5 and the red cell count to 3,000,000. On February 7, laparotomy was performed by Dr. Coffee.

Operation.—A rectus incision was made on the left side. The fascia was divided in the line of incision and the left rectus muscle split in the line of its fibers. The abdomen was explored manually. The spleen was studded with white nodules and was considerably enlarged. A splenule the size of a walnut was located at the hilus of the spleen and contained several caseating nodules. The spleen was attached to the lateral parietal peritoneum and the diaphragm by filmy adhesions. The tail of the pancreas was located between the posterior surface of the hilus of the spleen and the anterior surface of the left kidney. Both kidneys were normal to palpation. The liver was enlarged 3 fingerbreadths below the costal margin. There was a nutmeg appearance of the surface, and there were some areas of capsular fibrosis. There was no evidence of nodulation or caseation in the liver. The stomach, the large and small intestine and the peritoneum appeared normal. The spleen was freed from



Fig. 2.—Microscopic section showing tuberculosis of spleen. Giant cells are clearly seen.

adhesions to the left lateral parietal peritoneum and diaphragm by blunt dissection with the fingers. It was thereby mobilized, rotated medially and delivered into the wound. The gastrosplenic ligament was clamped, cut and ligated. The splenic pedicle was then doubly clamped, cut and ligated. The tail of the pancreas was carefully separated from the under surface of the spleen. The spleen was thereby severed from all its abdominal connections and removed. Oozing from various divided adhesions was controlled with hot packs, and the wound was closed in layers. The skin was closed with dermal sutures and three silk retention sutures were inserted.

The report of the pathologist on the surgical specimen was as follows:

Gross Appearance.—The specimen consisted of a very large spleen measuring 21 by 16 by 10 cm. The external surface was noticeably hemorrhagic, and the gross contour of the organ was distorted by a nodular formation. The splenic capsule was irregularly thickened, cyanosed and hemorrhagic. Numerous white subcapsular areas were noted. On section, the organ seemed to be involved by a caseofibrotic process which grossly appeared to be tuberculous. The process seemed to originate in numerous focal areas and to radiate from these

areas in all directions. Each focus of infection produced nodular deformation of that portion of the spleen. The intervening splenic tissue was beefy red, with considerable intervening edema and the gross appearance of interstitial hyperplasia.

Microscopic Appearance.—The section consisted of a portion of spleen presenting a definite distortion of the normal architectural pattern. Large areas of the tissues had undergone necrosis with adjacent infiltration by round cells and Langhans giant cells. The appearance of the process was typically that of tuberculosis. A diagnosis of tuberculosis of the spleen was made.

The postoperative course was stormy, with high fever, profuse perspiration, malaise and anemia. The patient was treated with repeated transfusions, adequate diet, vitamins and ultraviolet radiation to the abdomen and neck. From July 9 until August 5, the date of his discharge from the hospital, he was ambulatory and completely afebrile. He did, however, exhibit persistent tachycardia, and the hemoglobin content of his blood never rose above 79 per cent, with a red cell count of 4,140,000. Ultraviolet radiation to the neck resulted in a noticeable diminution in the size of the lymph glands. During the patient's postoperative bouts of fever, roentgenograms of the chest were made, but no evidence of miliary tuberculosis was present. The patient gained 13 pounds (6 Kg.) in weight. Although it was felt that he

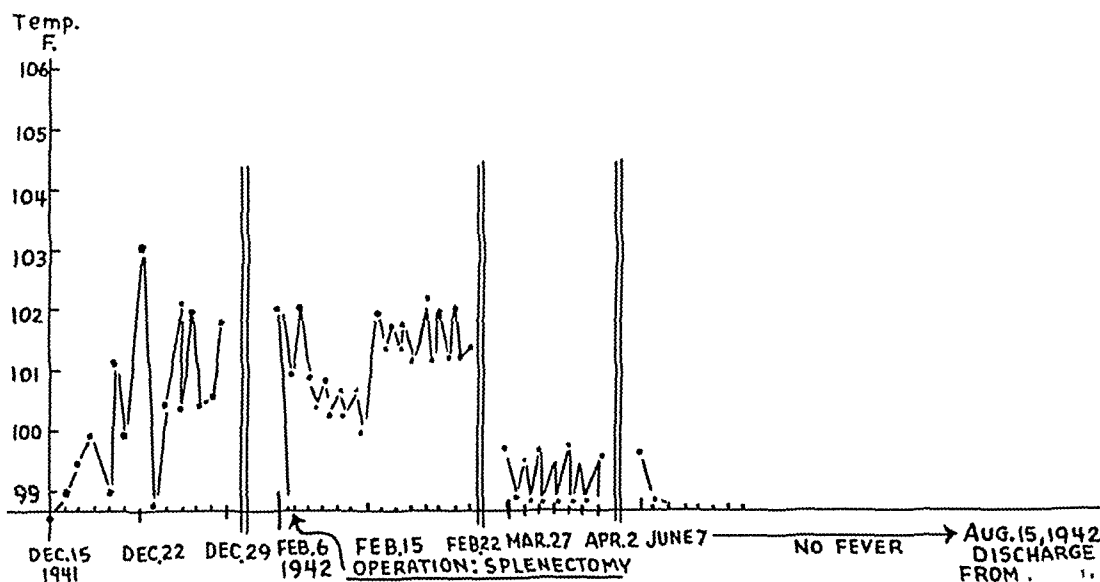


Fig. 3.—Samples of temperature range before and after splenectomy.

would benefit by further care in a sanatorium, he did not desire extended hospital treatment and therefore was discharged.

The patient's condition was considered improved. The presence of tuberculosis in the liver was never demonstrated, and the tuberculosis of the glands in the neck was considered to have subsided. Attempts to communicate with the patient by mail for follow-up were unsuccessful.

SUMMARY

A brief review of the essential nature of primary tuberculosis of the spleen is presented.

Splenectomy is the means of removing an active focus of tuberculous infection and preventing further hematogenous spread.

We present a report of a case of tuberculosis of the spleen in which improvement followed splenectomy.

Supportive therapy in the form of transfusions, adequate diet, vitamins and ultraviolet radiation is an important adjunct to surgical treatment.

Veterans Administration Facility.

PROGRESS IN ORTHOPEDIC SURGERY FOR 1942

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE AMERICAN
ACADEMY OF ORTHOPAEDIC SURGEONS

VIII. AMPUTATIONS, APPARATUS AND TECHNIC

PREPARED BY J. WARREN WHITE, M.D., GREENVILLE, S. C.

Amputations.—Literature pertaining to war surgery continues to be extensive as one would expect, and as was the case last year many articles on amputation have appeared. Nothing has been published this year, however, that has been on as high a technical or literary plane as those contributions mentioned in "Progress in Orthopedic Surgery for 1941." A somewhat similar but much briefer compendium was published as War Memorandum No. 5 by the Medical Research Council of the British War Wounds Committee²²³ during this last year and deserves mentioning as much for its brevity as for the practical information it contains. Nothing particularly new is emphasized, except possibly that consultation with an associate should be required before amputation is performed. The type of amputation should depend on (a) the time elapsed since the injury, (b) the level of the injury and (c) the general condition of the patient. This article has served as a pattern for others of the same nature. Two of the five members of this Subcommittee on Amputations have written separate articles, each enlarging somewhat on his phase of the subject, and one of these will be mentioned shortly. The two controversial subjects, end bearing and nerve treatment, were not discussed in this official government publication, and it is evident that the last word on these two points has not been said. When a British authority like Gordon-Taylor²²⁴ maintains that a nerve should be cut squarely across and not pulled down, ligated or subjected to injections, while the newly appointed Surgeon General of the Army,²²⁵ a long time authority on amputations, in an excellent article advocates just the opposite, the occasional amputator is justifiably considerably confused and might therefore conclude that it does not make much difference, except under certain conditions. An example of such a condition is a high tibial amputation, in which the retraction and cutting of a nerve would be likely to place the inevitable terminal neuroma in a weight-bearing location. The value of the so-called guillotine operation in severe compound injuries requiring amputation is extolled by all authors,²²⁶ if operation is delayed twenty-four hours and performed so as to make a concave surface and avoid the distressing "lead pencil" stump. Traction on skin is universally insisted on. Kirk²²⁵ calls attention to the ease of doing a late plastic closure when a guillotine amputation had been performed an average of four months before.

Another controversial point about amputations is the treatment of the end of the bone. Kirk²²⁵ states that the bone should be sawed through without doing anything to the periosteum except to traumatize it as little as possible and cut it completely around—not sew it over the end or skin it back, as was advocated

223. Emergency Amputations, Medical Research Council War Memorandum no. 5. abstracted, War Med. 2:147-153 (Jan.) 1942.

224. Gordon-Taylor, G.: Ten Commandments in Amputation, Lancet 1:669 (June 6) 1942.

225. Kirk, N. T.: Amputations in War, J. A. M. A. 120:13-16 (Sept. 5) 1942.

226. Footnote 223. Gordon-Taylor,²²⁴ Kirk.²²⁵

formerly. Schmorell²²⁷ advocates the covering of bone surfaces with periosteum, admittedly with sound physiologic reasoning, except that there is always a suture line of the periosteum, and there is no guaranteeing that an osteophyte will not grow there.

[ED. NOTE.—One of the editors (J. W. W.) feels that this is an unnecessary requirement and unjustifiably prolongs an operation in which time is frequently so valuable.]

Seven articles on the use of refrigeration in amputations have been reviewed,²²⁸ which is an indication of the growing popularity and interest of this relatively new technical method in amputations. Nothing new has been brought out, except that fear of frostbite damage to skin is unjustified in view of a case report by McElvenny,^{228f} for whose patient, a 70 year old man, refrigeration was employed for twenty-eight days without ill effect. For those wishing to try this anesthetic agent, the specifications of an efficiently functioning refrigeration box have been published by Gordon.^{228e} This method is obviously still in the experimental stage, but progress is definitely being made. It is satisfactory that so many surgeons are interested, in order that a safe practical technic may be worked out for occasional amputators, as so many surgeons are. The value of real refrigeration for intractable pain, particularly of the extremities, is being emphasized by this investigative work, and its local application with ethyl chloride is discussed by two British authors.²²⁹ These authors claim that immediate relief has been obtained in various diseases of the soft tissues, from de Quervain's tenosynovitis to pain in the lower part of the back.

[ED. NOTE.—These articles must be read reservedly, but they do call attention to a therapeutic agent that heretofore has been little used. No damage is done by judicious, temporary superficial freezing of the skin. As an office "stunt" for certain impressionable patients with a low pain threshold, one can imagine it to be of considerable and at least temporary value. To many, it might smack a little of empiricism, but occasions for its use might appear sufficiently often to justify having a tube or so in the office.]

Thorek²³⁰ has described for a low thigh amputation a technic simulating a guillotine procedure, except that sufficient bone is removed to permit end closure in layers without drainage after careful hemostasis. A tourniquet is not used, since the femoral vessels are accessible for easy ligation when the circular incision is made just above the knee after the inner hamstrings are cut. This amputa-

227. Schmorell, H.: Covering of Bone Surface in Stumps of Long Bones with Periosteum, *Zentralbl. f. Chir.* **68**:1912-1913 (Oct. 11) 1941.

228. (a) Allen, F. M.: Reduced Temperatures in Surgery: Experiments on Pelvic and Abdominal Refrigeration with Especial Reference to Traumatic and Military Surgery, *Am. J. Surg.* **55**:451-466 (March) 1942. (b) Crossman, L. W.; Ruggiero, W. F.; Hurley, V., and Allen, F. M.: Reduced Temperatures in Surgery: Amputations for Peripheral Vascular Disease, *Arch. Surg.* **44**:139-156 (Jan.) 1942. (c) Schiebel, H. M.: Use and Evaluation of Anesthesia by "Freezing" for Surgery of Extremities in Diabetic Patients, *North Carolina M. J.* **3**:227-229 (May) 1942. (d) Crossman, L. W., and others: Refrigeration Anesthesia, *Anesth. & Analg.* **21**:241-254 (Sept.-Oct.) 1942. (e) Gordon, J. D.: Refrigeration Box for Amputation, *Am. J. Surg.* **58**:453-455 (Dec.) 1942. (f) McElvenny, R. T.: Present Status of Cooling Limbs in Preparation for Surgical Procedures, *ibid.* **58**:110-112 (Oct.) 1942. (g) Smith, W. E.: Refrigeration of Gangrenous Extremities Before Amputation, *Ohio State M. J.* **38**:826-829 (Sept.) 1942.

229. Henry, A. K.: Freezing with Ethyl Chloride to Relieve Pain and Loss of Movement, *Lancet* **2**:280-281 (Sept. 5) 1942. McIntosh, C. A., and Petrie, J. G.: Use of Ethyl Chloride Spray in Soft-Tissue Injuries, *ibid.* **2**:279-280 (Sept. 5) 1942.

230. Thorek, P.: Simplified Technic for Thigh Amputation, *Surg., Gynec. & Obst.* **75**:225-228 (Aug.) 1942.

tion is more on the order of the Callander technic, which is discussed favorably by Brown,²³¹ who cites 21 consecutive operations without a postoperative death on patients ranging in age from 39 to 82. The one drawback to this amputation is its unpopularity with makers of artificial limbs, who ordinarily can fit a prosthesis better to a shorter stump.

During the last year, three more articles²³² on interinnominoabdominal amputations have been published, an indication that a few are still interested in this radical procedure. No new points are brought out that have not been thoroughly discussed in previous articles, and the procedure must be reserved for the rare and special cases fulfilling the rigid requirements for the consideration of such a radical operation.

Pack, McNeer and Coley²³³ report a series of 31 consecutive cases of interscapulothoracic amputation for malignant tumor. Only 6 of the patients have survived. Although this very major surgical procedure has a greater usefulness than the interinnominoabdominal amputation, the need for its performance fortunately arises relatively seldom. One hundred and forty-one cases have been cited in the literature since 1900. The surgical technic originated by Berger, as well as those recommended by Kocher and by Littlewood, is discussed, but no radical modifications of any of these are advocated.

Surgical Technic.—Goodwin and Cameron²³⁴ have reported success in using a pair of interdependent bone-holding forceps devised to aid in the open reduction of fractures and in maintaining apposition even in the oblique spiral fracture which is so common in the lower part of the tibia. Wire threaded through holes in the fragments drilled through the slotted jaws of the clamp maintains apposition with a minimum of material. The two supplementary instruments used for passing the wire loops through the hook arrangement are useful wherever wire or other material is to be passed through bone.

[ED. NOTE.—For surgeons partial to the use of wire for fixation, this instrument should be most useful.]

Farill²³⁵ describes a subcutaneous method of lengthening the heel cord by using an especially devised knife which cuts the tendon longitudinally as well as transversely to make the Z tenotomy usually made at open operation. This is an ingeniously conceived procedure devised because of the difficulty in getting tendon elongation by alternate transverse incisions subcutaneously.

[ED. NOTE.—One of the editors (J. W. W.) recently published a description of a technic which has been employed for several years in which account is taken of the rotation of the heel cord. By judiciously placing the transverse subcutaneous incisions through two thirds of the cord at appropriate levels with an ordinary tenotome, the structure can be elongated without the longitudinal cut for which the special knife is necessary. In this way all the fibers are cut, and the tendon

231. Brown, J. R.: Low Thigh Amputation by Callender Method, *M. Bull. Vet. Admin.* **18**:237-240 (Jan.) 1942.

232. Morton, J. J.: Interinnomino-Abdominal (Hindquarter) Amputation, *Ann Surg.* **115**: 628-646 (April) 1942. Whittaker, A. H.: Interinnomino-Abdominal Amputation, *Indust. Med.* **11**:1-3 (Jan.) 1942. Whittaker, A. H., and Sobin, D. J.: Interinnomino-Abdominal Amputation, *Ann. Surg.* **115**:435-440 (March) 1942.

233. Pack, G. T.; McNeer, G., and Coley, B. L.: Interscapulothoracic Amputation for Malignant Tumors of Upper Extremity, *Surg., Gynec. & Obst.* **74**:161-175 (Feb.) 1942.

234. Goodwin, F. C., and Cameron, D. M.: Bone-Holding-Drilling Forceps, *Southwestern Med.* **26**:228-229 (July) 1942.

235. Farill, J.: Elongation of Achilles Tendon by Author's Technic in Therapy of Pes Equinus, *Gac. méd. de México* **72**:69-72 (Feb. 28) 1942.

gives way as would a manila rope if one had cut it partially through at different levels, making certain that all the strands were cut either above or below.]

Wassersug²³⁶ has supplied a long felt want in suggesting a new marker for cutaneous localization which will be permanent and useful both for roentgen examination and surgical procedures. It is designed particularly, of course, for operations on the spine. A 1 per cent suspension of lampblack in iodized poppyseed oil is injected subcutaneously and intramuscularly where localization is needed.

Attention is called by Breck and Basom²³⁷ to the value of a tourniquet on the leg when bone for grafting is removed from the tibia and cites the advantages of the Campbell-Boyd pneumatic tourniquet for this purpose.

[ED. NOTE.—I have made use of this idea as have many others for years and suggest that it be employed when pinch grafts are needed for extensive burns in order to conserve blood in those usually extremely debilitated patients.]

Bell²³⁸ justifiably advocates the use of alloy steel wire in general surgery, citing its various advantages but admitting that it is somewhat more difficult to use.

[ED. NOTE.—Many, including Bunnell, who has used it particularly in operations on tendons, have advocated it for years, and it is felt that progress in orthopedic surgery will follow its more extensive use. Bell gives the name of the manufacturer.]

The early disappearance of kangaroo tendon used for repair of tendons as reported by Trethewie and Williams²³⁹ discourages its use as suture material in tenoplasties and may serve to explain the poor results in many cases in which it has been used.

[ED. NOTE.—As it has been frequently proved that good tendon repair takes place in four to six weeks, some doubt may arise relative to placing the blame on the kangaroo tendon material. The error probably frequently is due to inadequate original fixation. Silk seems to be the generally accepted material in such instances. It is much easier to handle; the knots are more likely to hold, and it is permanent.]

The importance of only three weeks' immobilization in tenodeses is advocated by Kernwein.²⁴⁰ As a result of animal experimentation, he has found that after three weeks prolonged protection retards the development of tensile strength.

[ED. NOTE.—This seems to be a little short in view of reports of similar experiments, and it is felt that adding another week would do no particular harm.]

The fact that unfavorable reaction of the tissues to dissimilar alloys is not simply due to electrolytic action but to the physical and chemical properties of the metals themselves is discussed by Bothe and Davenport.²⁴¹ They state that solubility and the degree of toxicity of the dissolution products appear to be the

236. Wassersug, J. D.: New Marker for Spine Surgery, *J. Bone & Joint Surg.* **24**:464-465 (April) 1942.

237. Breck, L. W., and Basom, W. C.: Use of Campbell-Boyd Pneumatic Tourniquet for Spine Fusion Procedures, *J. Bone & Joint Surg.* **24**:461 (April) 1942.

238. Bell, R. H.: Impressions Concerning Use of Alloy Steel Wire in General Surgery, *Mil. Surgeon* **91**:185-187 (Aug.) 1942.

239. Trethewie, E. R., and Williams, E.: Use of Kangaroo Tendon for Muscle and Tendon Suture, *Australian & New Zealand J. Surg.* **11**:207-208 (Jan.) 1942.

240. Kernwein, G. A.: Study of Tendon Implantations into Bone, *Surg., Gynec. & Obst.* **75**:794-796 (Dec.) 1942.

241. Bothe, R. T., and Davenport, H. A.: Reaction of Bone to Metals: Lack of Correlation with Electrical Potentials, *Surg., Gynec. & Obst.* **74**:231-235 (Feb.) 1942.

chief factors. They consider that such constituents as nickel, copper or manganese are toxic and should be avoided. They feel that vitallium comes near to meeting the requirements for a nonirritating substance but hope the rarer metal tantalum will be even better after it has been given a trial.

Venable,²⁴² in discussing factors in the choice of material for bone plates and screws, advises avoidance of the use of plaster whenever possible, implying that its mere use unnecessarily prolongs convalescence.

[ED. NOTE.—It is feared that statements of this nature by an enthusiast for internal fixation are too prone to influence surgeons less experienced in open technic, to the detriment of their patients. It is believed that the time is appropriate for the writing of some papers discussing improvements in the use of plaster casts, which by and large throughout the country is justifiably the method of treatment by the general surgeon. It is recalled that one such article, that of Clarke,²⁴⁵ appeared last year.]

A French article by Verhe, Menegaux, Verne and Magnant²⁴³ discusses the importance of selecting correct material and states that apparently there were only three steel alloys available in occupied Paris at the time of writing. A point that is brought out which seems reasonable is that hammering or forging should be avoided in the construction of plates and that they should have a high polish. The authors mention that care should be taken not to scratch the plates, but they are inconsistent in stipulating that the type of metal should be imprinted on the prosthesis.

Speed²⁴⁴ has published a twenty page detailed article giving his mature ideas on the technic of open reduction and internal fixation. While no new points are mentioned, it is an excellent article by a past master and includes up to date and generally accepted ideas on this subject. It is a creditable discussion demonstrating the progress that has been made in the refinement of the technic for open reductions.

Plaster Technic.—Clarke²⁴⁵ has written from England an excellent and refreshing résumé of plaster technic discussing the advantages of skin-tight plaster casts and stating that sores result more from friction than from pressure. He believes that the application of plaster casts directly to the skin is one of the major advances of recent years.

[ED. NOTE.—Much sound advice is given, but he does not mention the necessity of carrying the plaster to the end or very close to the end of an extremity to avoid a possible circulatory bottleneck. He calls attention to the value of 2 per cent borax in plaster water as an agent for delaying the time of setting of plaster without detrimental effect apparently to the strength of the final cast. He extols the Trueta "pattern-plasters" as time savers even in the application of such large casts as shoulder and hip spicas.]

A note of warning has been sounded by Archibald,²⁴⁶ a Canadian, relative to the use of the sulfonamide compounds in war surgery. No chemotherapy, local

242. Venable, C. S.: Factors in Choice of Material for Bone Plates and Screws, Surg. Gynec. & Obst. **74**:541-545 (Feb., no. 2A) 1942.

243. Verne, J.; Menegaux, G.; Verne, J. M., and Magnant, J. B.: Tolerance for Certain Steels Used in Buried Prosthesis: Study of Osteosynthesis, Presse méd. **49**:452-455 (April 29) 1941.

244. Speed, K.: Technic of Application of Metal Plate to Oblique or Spiral Fracture of Long Bone, S. Clin. North America **22**:83-102 (Feb.) 1942.

245. Clarke, R.: War Surgery of Extremities: Plaster Technic, Brit. M. J. **1**:797-800 (June 27) 1942.

246. Archibald, E. W.: Casts New and Old in War Surgery (of Arms and Legs), Canad. M. A. J. **47**:93-102 (Aug.) 1942.

or otherwise, can be a substitute for early (within six hours) and thorough cleaning and débridement. When this has been done the closed plaster method is far superior to any method requiring splinting and frequent dressing.

Two articles have been published on facilitating the removal of casts, one by Roath²⁴⁷ describing another electric cast cutter, which in view of previous experience with such instruments must prove its value by performance, and another by Price,²⁴⁸ an Englishman, who suggests simply the pulling through of 24 gage piano wire under a cast by a petrolatum-smear cotton tape laid on the skin prior to the application of the plaster. The cutting is completed according to the Bickford method of forcing the wire through the cast with a specially devised twister.

Galewski,²⁴⁹ a Russian writing in England, advocates the use of a special silicate solution instead of plaster. Because of its lightness and toughness he believes it to be particularly appropriate for walking apparatus. To shorten its drying time, which is the drawback with all the silica preparations, he advocates local use of heat. It is feared that it is just another slowly drying material and therefore an impracticable substitute for the time-tested plaster, but more will doubtless be heard of it if it proves to be as valuable as is claimed.

The Council on Physical Therapy²⁵⁰ has approved what is called a "cruricast bandage," a zinc gelatin paste being employed as the stiffening material. For office use it apparently is superior to a dressing prepared with soft paste of zinc oxide N. F. and has the same indications. It is claimed to be a "compressive and supportive dressing which is soft and resilient. This dressing is porous, to allow perspiration and evaporation, and is of sufficient strength to prevent expansion from pressure of body heat." As a dressing for application after the removal of a cast for those who feel the need of more support than is given by simple elastic woven bandages, it should be better than a dressing made with paste of zinc oxide and well worth trying.

Galland²⁵¹ describes a long-looked-for ischial seat brace for spica application. Such a device is needed particularly for the obese patient. It is hoped that one of the manufacturing houses will have this equipment on sale in the near future if they do not have it already. If it possesses only a few of the good qualities claimed, it will be an improvement on the conventional support that has been used over the years.

An almost complete elimination of the odor in the Orr treatment of osteomyelitis has been obtained by Wallis and Dilworth²⁵² with a dressing impregnated with an 18 per cent solution of lactose. This supplies an easily oxidizable carbohydrate for the putrefactive bacteria to work on, thus eliminating the production of the foul-smelling products of putrefying protein. As a result, casts can stay on longer, with more benefit to the patient. Another article on the elimination of odor in osteomyelitis was written by two English surgeons, Seddon and Florey,²⁵³ who use cloth bags impregnated with carbon dust to put the offending part in. The

247. Roath, C. A.: Electric Cast Cutter, *California & West. Med.* **56**:78-79 (Feb.) 1942.

248. Price, C. W. R.: Removal of Plaster Casts: Modification of Bickford Method, *Brit. M. J.* **2**:772 (Nov. 29) 1941.

249. Galewski, S.: "Liquid Plaster" for Immobilization, *Brit. M. J.* **1**:225 (Feb. 14) 1942.

250. Cruricast Bandage Acceptable, report of the Council on Physical Therapy, *J. A. M. A.* **118**:456 (Feb. 7) 1942.

251. Galland, W. I.: Improved Ischial Seat Brace, *J. Bone & Joint Surg.* **24**:204-205 (Jan.) 1942.

252. Wallis, A. D., and Dilworth, M. J.: Odor in Orr Treatment: Prevention by Lactose, *J. A. M. A.* **120**:583-587 (Oct. 24) 1942.

253. Seddon, H. J., and Florey, H. W.: Filter Cloth for Controlling Smell from Plasters, *Lancet* **1**:755 (June 27) 1942.

material is called filter cloth, but nothing is mentioned as to where it may be obtained. In any event, the deodorizing quality of carbon has been employed and evidently found effective. It seems like a satisfactory alternative method to the use of lactose solution when redressing seems inadvisable.

New Splints and Apparatus.—A cleverly devised folding Thomas splint is described by Hosken²⁵⁴ of England which, if it functions as efficiently as is claimed, is ideal for front line use. Its chief value lies in its portability and ease of application, for which real advantages strength has unquestionably been sacrificed. It would therefore be unsuitable for general civilian use.

Cohen²⁵⁵ has devised a volar flexion splint which should be of value in preventing and correcting the distressing metacarpophalangeal hyperextension deformity. A principle not employed in other apparatus devised for the same purpose is used. It is apparently an efficient splint and should be investigated by those not satisfied with their present equipment.

Sponge rubber bandaged to the leg is advocated as an efficient means for traction by Barnard,²⁵⁶ particularly when local physical therapy is desired or there is some other indication for frequent removal. It is felt that this is a means of obtaining traction well worth adding to one's armamentarium.

An instance of applying another carpenter's tool to surgical technic is suggested by Nicola,²⁵⁷ who recommends a spirit level. Unfortunately, no information is given as to how to obtain the proper type of level, which apparently has to be specially made.

[ED NOTE.—One wonders if the same excellent idea might be carried out with an inverted protractor incorporating a small hanging plumb bob.]

Criticism might be directed to an apparently efficient light fracture frame devised by Cleary²⁵⁸ because a single pin is used in either fragment. It has many commendable features in addition to its avoidance of the cumbersomeness of the usual commercial equipment.

Ainsworth-Davis lays justifiable emphasis on the avoidance of metacarpophalangeal hyperextension²⁵⁹ in another English paper in which he describes a steering wheel apparatus for grasping exercises for severely cicatrized hands. The apparatus is readily duplicated by a mechanic to whom old automobile parts are accessible. It would be a novel and useful device suitable to the physical therapy department of a large military hospital.

Several commendable new splint ideas have been reported of interest, particularly to the military surgeon, who has to improvise extensively, but do not contain sufficient new material to mention specifically and for lack of space have had to be left out. Among the best of these are Elliot's²⁶⁰ "drop wrist" splint, Slocum's²⁶¹ shoulder abduction splint and Wilson's²⁶² modification of the banjo splint for fractures of the fingers and toes.

254. Hosken, J. G. F.: Folding Thomas Splint, *Brit. M. J.* **1**:187 (Feb. 7) 1942.

255. Cohen, H. H.: Adjustable Volar-Flexion Splint, *J. Bone & Joint Surg.* **24**:189-192 (Jan.) 1942.

256. Barnard, H. I.: Rubber-Surface Skin Traction, *J. Bone & Joint Surg.* **24**:462-463 (April) 1942.

257. Nicola, T.: Use of Curved Spirit Level, *Am. J. Surg.* **57**:191-192 (July) 1942.

258. Cleary, E. W.: Light Fracture Frame: Uses and Construction, *J. Bone & Joint Surg.* **24**:694-698 (July) 1942.

259. Ainsworth-Davis, J. C.: Preservation of Function in Burnt Hand, *Brit. M. J.* **1**:724 (June 13) 1942.

260. Elliot, H.: Easily Made "Drop Wrist" Splint, *Canad. M. A. J.* **47**:363 (Oct.) 1942.

261. Slocum, D. B.: Simple Abduction Splint for Upper Extremity, *Mil. Surgeon* **91**:26-29 (July) 1942.

262. Wilson, C. S.: Modification of Banjo Splint, *Canad. M. A. J.* **46**:585-586 (June) 1942.

A most useful and sure method of removing a ring from a swollen finger without cutting the ring is reported by Arbuckle.²⁶³ A piece of string is passed under the ring. The one end is held on the proximal side of the ring, and the part distal to the ring is wound tightly around the well soaped finger. The proximal end of the string is then unwound against the proximal edge of the ring and forces the ring down over the finger.

[ED. NOTE.—Try it. It's a good parlor trick anyhow, and soap is really not needed.]

Continued interest in the solution of the problem of discrepancy in length of the legs is evidenced by the appearance of seven new articles in 1942, all of them very good. The most important is the one by Gill and Abbott²⁶⁴ on a practical method of predicting growth of the femur and the tibia in children. While most readers would feel that the method is too complicated for practical use, the article is undeniably of great importance, and it should be carefully read by all who contemplate this fascinating surgical problem. It is most important in the timing and location of operations designed to arrest growth. Many distressing experiences may be avoided if problems of this nature are worked out in accordance with the recommendations contained in this article. Due consideration is given to the age of bone maturation as recorded by Todd²⁶⁵ in determining the probable age at which growth stops.

Howorth²⁶⁶ discusses the leg-shortening operation, particularly in relation to the literature and history of the problem of inequality in length of the legs, and reports 17 operations, 11 of them being step-cut osteotomies with plate fixation. The article is thorough but does not mention the stimulation to growth of the shortened leg in a growing child by this procedure, a fact which must always be kept in mind.

[ED. NOTE.—One of the editors (J. W. W.) has found in several instances in a series of over 80 cases that half of a 2 inch (5 cm.) correction in a growing child may be lost in the next year or two after such a procedure. He feels that it is an operation to be reserved only as a supplement to the operation for the arrest of growth when done before the age of bone maturation. The many time-consuming, traumatizing technics are more appropriate for the cabinet maker than for the surgeon. He recommends the simple overlap through and through screw fixation technic including all four strong, unweakened bone cortexes.]

Brockway and Fowler²⁶⁷ report their experience with 105 leg-lengthening operations. Excellent results were achieved in 65 per cent of the cases, while in 22 per cent more they were considered good. Protection had to be continued on an average of nine months. Bony union was present in 57 per cent of cases in nine months and in 100 per cent in two and a half years.

[ED. NOTE.—One of the editors (J. W. W.), who is an ardent leg shortener, feels that the dangers and complications were unjustifiably minimized in view of the experience of many other authors. He also feels that the authors have not given sufficient credit to the value of the growth arrest procedure and that sufficient

263. Arbuckle, M. F.: String Method of Removing Tight Ring from Swollen Finger, *Mil. Surgeon* 90:184 (Feb.) 1942.

264. Gill, G. G., and Abbott, L. C.: Practical Method of Predicting Growth of Femur and Tibia in Child, *Arch. Surg.* 45:286-315 (Aug.) 1942.

265. Todd, T. W.: Atlas of Skeletal Maturation, St. Louis, C. V. Mosby Company, 1937.

266. Howorth, M. B.: Leg-Shortening Operation for Equalizing Leg Length, *Arch. Surg.* 44:543-555 (March) 1942.

267. Brockway, A., and Fowler, S. B.: Experience with One Hundred and Five Leg Lengthening Operations, *Surg., Gynec. & Obst.* 75:252-256 (Aug.) 1942.

knowledge is available to perform this simple operation on growing children with as much certainty of success as can be expected with either the shortening or the lengthening procedure.]

Phalen and Chatterton²⁶⁸ discuss rather in detail the problem of discrepancy in length of the legs and conclude that in a great majority of cases shortening is the method of choice. They believe that the admittedly more formidable lengthening should be reserved for those unusual cases in which loss of height is of serious consequence, for example when there is a possibility of future military service, an important point during these times.

In all studies of discrepancy in length of the legs, a satisfactory method of recording length is necessary. Merrill²⁶⁹ describes a roentgenographic technic for the measurement of the actual size rather than the discrepancy in length of the long bones. The method is accurate but appears to be impracticable for clinical use and more suited to particular research problems, such as are encountered in experimental work on animals.

Irradiation as an agent in retarding bone growth is discussed by Kaplan,²⁷⁰ who reports only 1 case, in which in twenty-eight months a discrepancy of $2\frac{1}{2}$ inches (6.5 cm.) was reduced $\frac{3}{4}$ inch (2 cm.). It is apparent that much more research work must be done along this line before any safe and practical method can be recommended.

Flecker²⁷¹ has published a long article discussing growth of bone and the time of appearance and fusion of centers of ossification as observed by roentgenographic methods. He has found that several errors, of little practical importance to the orthopedic surgeon, however, are given in various tables. It is an excellent, thorough article of little practical interest, except to those orthopedic surgeons doing research work on bone growth. No serious discrepancies were noted in this paper when it was compared with the excellent chart by Camp and Cilley²⁷² of the Mayo Clinic, which appeared twelve years ago and which should hang beside every x-ray viewing box.

IX. TUBERCULOSIS OF BONES AND JOINTS

PREPARED BY ALAN DE FOREST SMITH, M.D., NEW YORK, ASSISTED BY THE STAFF OF
THE NEW YORK ORTHOPAEDIC DISPENSARY AND HOSPITAL

Harris and Coulthard²⁷³ have made an important study of 307 cases of tuberculosis of bones and joints treated in an institution in Toronto during the ten years from 1931 through 1940. They were able to follow 296 patients who were discharged from the hospital. The majority of these patients were adults. The diagnosis was proved bacteriologically in 70 per cent of the cases, and care was taken to exclude all in which there was any doubt of the cause.

268. Phalen, G. S., and Chatterton, C. C.: Equalizing Lower Extremities: Clinical Consideration of Leg Lengthening Versus Leg Shortening, Surgery **12**:768-781 (Nov.) 1942.

269. Merrill, O. E.: Method for Measurement of Long Bones, Am. J. Roentgenol. **48**:405-406 (Sept.) 1942.

270. Kaplan, I. I.: Irradiation in Treatment of Limb Asymmetry, Arch. Pediat. **59**:559-564 (Sept.) 1942.

271. Flecker, H.: Time of Appearance and Fusion of Ossification Centers as Observed by Roentgenographic Methods, Am. J. Roentgenol. **47**:97-159 (Jan.) 1942.

272. Camp, J. D., and Cilley, E. I. L.: Diagrammatic Chart Showing Time of Appearance of Various Centers of Ossification and Period of Union, Am. J. Roentgenol. **26**:905 (Dec.) 1931.

273. Harris, R. I., and Coulthard, H. S.: Prognosis in Bone and Joint Tuberculosis: Analysis of Results of Treatment and Consideration of Factors Which Influence End Result, J. Bone & Joint Surg. **24**:382-395 (April) 1942.

All patients were treated by preliminary rest, which was followed by an operation to produce arthrodesis, except when it was contraindicated by advanced pulmonary lesions or other complications. The intent of the study was to discover the factors affecting the prognosis. It was concluded that active pulmonary tuberculosis, secondary infection of an abscess with sinuses and multiple tuberculous lesions, in that order, were the most important. Of the 296 patients, 28.6 per cent had multiple lesions elsewhere than in the lungs. Such lesions were chiefly in other bones. They retarded recovery and often necessitated several operations but did not greatly affect the mortality. Renal tuberculosis was found in 23 per cent. This also was not extremely serious as far as life was concerned. Secondary pyogenic infection in tuberculous abscesses, usually caused by improper treatment previous to admission, accounted for many fatalities and operative failures. Pulmonary tuberculosis was the gravest of all the complications. Whereas of those patients having no other than the bone lesion only 4 per cent died, of those having pulmonary tuberculosis from 20 to 80 per cent died, depending on the grade of pulmonary lesion. Forty per cent had pulmonary involvement. Eighty per cent of the patients with uncomplicated tuberculosis of the spine and 100 per cent of those with uncomplicated tuberculosis of the knee were cured and returned to work after arthrodesis. Of the 296 patients followed after discharge from the hospital, 28.6 per cent died. Ninety-six per cent of the deaths were caused either by some form of tuberculosis or by secondary infection of an abscess.

There was no evidence that the disease was disseminated by operation in any case. The type of infection was determined by culture, and not a single case of bovine tuberculosis was found.

[ED. NOTE.—This is a valuable study which confirms the conclusions which have been derived from other careful analyses of larger series of cases.]

Badgley and Hammond²⁷⁴ report a review of 76 patients who had proved tuberculous arthritis of 77 hip joints and who had an arthrodesis as part of their treatment at the hospital of the University of Michigan Medical School between 1925 and 1935. The proof was obtained by pathologic and bacteriologic studies of tissue or material removed at operation or of pus from a cold abscess originating from the hip joint at some time during the patient's treatment. The age at the time of operation varied from 2 to 56 years. Almost two thirds of the patients (64 per cent) were between 6 and 20 years old.

The present plan of preoperative treatment consists of measures to build up the patients' general health and of immobilization to afford complete rest of the hip. These are continued until the general condition is good, until all other foci of tuberculosis are quiescent and until the patient has demonstrated his ability to combat the hip tuberculosis successfully. In the earlier years covered by this report, the arthrodesis was performed soon after the diagnosis was made, so that only 61 per cent of the patients in this series had preoperative care consistent with the aforementioned standards.

The types of operation were as follows: extra-articular, 53 per cent; intra-articular with extra-articular grafts, 30 per cent, and intra-articular, 14 per cent. The Hibbs operation constituted 60 per cent of the extra-articular procedures. Shock occurred in 4 cases and caused death in 2 (3 per cent). The average time for complete immobilization in plaster after operation was ten months, and with plaster followed by some other form of splinting, nineteen months. A second

274. Badgley, C. E., and Hammond, G.: Tuberculosis of Hip: Review of Seventy-Six Patients with Proved Tuberculous Arthritis of Seventy-Seven Hips Treated by Arthrodesis, *J. Bone & Joint Surg.* 24:135-147 (Jan.) 1942.

arthrodesis was performed on 12 patients, or 16 per cent, because of failure of the first operation. In those in whom ankylosis of the hip developed, the average time required for clinical ankylosis was fifteen months and for bony ankylosis, as demonstrated by roentgenograms, sixteen months.

The end results are based on the history and the clinical and roentgenographic examinations. The average time from operation to final symptom examination (questionnaire) was seven years and five months; and between operation and final clinical and roentgenographic examination, five years. Both the subjective and the objective end results were considered, and the final classification of the patient represents a composite picture of the two. On this basis good results were obtained in 52 per cent, fair in 22 per cent and poor in 8 per cent. The total mortality was 18 per cent. The result was unknown in 5 patients. In all the 6 patients (8 per cent) who obtained a poor result, ankylosis was absent, and two thirds had secondary pyogenic infection of the hip with formation of sinuses and recurrent abscesses. Of the deaths, 8 per cent were due to unrelated diseases or unknown causes, 3 per cent to operative shock and 7 per cent to tuberculosis.

From careful studies of each case, certain factors were found which seemed to be important in relation to the outcome. Among them were the following:

1. Preoperative care of six months or longer was associated with much better results.

2. If the arthrodesis was not done before the age of 8 years or after the age of 30 the outlook was more favorable.

3. The presence of active pulmonary tuberculosis or of a sinus or cold abscess at the time of operation was associated with more unfavorable results.

4. If during the preoperative treatment the serial roentgenograms revealed improvement in appearance or progression in destructive changes followed by improvement, the prognosis was better.

5. The type of arthrodesis performed did not apparently influence the end result except in the case of intra-articular arthrodesis without bone grafts.

The authors propose from this study an optimum time for arthrodesis. There should be six months or more of preoperative treatment, which should be continued until (1) the patient is at least 8 years old; (2) any abscess or sinus about the joint has disappeared; (3) there is no evidence of active pulmonary tuberculosis, and (4) there is roentgenographic evidence of improvement in the lesions.

[ED. NOTE.—The results of the series parallel quite clearly those in patients treated at the New York Orthopaedic Hospital, where only 66 per cent of the primary operations produced a bony fusion. By doing second and third operations on the remainder the number of successful results was raised to nearly 90 per cent. No single operative technic is applicable to all cases. The procedure must be adapted to the patient.]

Roth²⁷⁵ presents a follow-up study of patients on whom an arthrodesis of the hip joint was performed for tuberculosis. One hundred and eleven patients with clinical tuberculosis of the hip joint were seen at the Hospital for Joint Diseases in New York city from 1928 to 1940. Fifty of these had an arthrodesis performed, and of these 4 were discarded from the study because of inadequate records and 1 because of doubt of the diagnosis. For 27, or 60 per cent, of the remaining 45 hips the diagnosis was proved by bacteriologic or histologic examination. Five

275. Roth, F. B.: Results Following Arthrodesing Operations for Tuberculosis of Hip, *Bull. Hosp. Joint Dis.* 3:153-162 (Oct.) 1942.

of the patients had more than one clinically apparent focus of tuberculosis, 1 in the lungs, 1 in the opposite hip and 3 in the lumbar portion of the spine.

Fifty-seven arthrodeses were done on the 45 patients. Ten of these were secondary and 2 were tertiary procedures. An extra-articular arthrodesis was performed in 93 per cent of the cases and a combined extra-articular and intra-articular operation was done in 5 per cent. In 1 patient, tibial grafts were driven through the neck of the femur into the acetabulum.

A preoperative program of conservative care of from six to twelve months was carried out for the majority of children but only for a minority of the adults. Such a program is considered worth while for children, as it usually leads to an improvement in the local and the general condition of the patient.

Firm bony union was judged to have occurred when there was no longer any doubt as to its presence. Nineteen, or 61 per cent, of the 31 hips fused after one operation. This figure was raised to 24, or 77 per cent, by secondary arthrodeses and to 26, or 84 per cent, by tertiary arthrodeses.

Poorer results were obtained in those patients that had local abscess formation at the time of operation. The average times for fusion were nineteen months for the patients who had had a local sinus within the year before operation, forty-two months for those with local abscesses and sixteen months for those without complications. About three quarters of the operations were done before the patients were 17 years old. No patient operated on before the age of 6 obtained a fusion. If the 5 patients that had an additional focus of disease are excluded, postoperative sinuses developed within three months after 23, or 44 per cent, of 52 operations. All but 9 of the 23 obtained complete healing of the skin during observation. There was no immediate operative mortality in this group of 40 patients, but several deaths occurred later. One patient died two months after arthrodesis from tuberculous meningitis and miliary tuberculosis. Two died after five months and thirteen years respectively from secondary infection of the hip subsequent to a postoperative sinus, and 1 died after six and one-half years from infection of the genitourinary tract subsequent to a secondary infection of the hip originating in a postoperative sinus.

[ED. NOTE.—Although arthrodesis is more difficult in the tuberculous hip of a child under 6 years of age, it has been done successfully in many young children. Because of the disastrous consequences of other methods of treatment in such patients we believe that the operation should be performed whenever the patient's condition permits, regardless of age.]

After commenting generally on tuberculous joints and mentioning the methods of iliofemoral arthrodeses of Albee, Hibbs and Wilson and the ischiofemoral technics of Trumble and Brittain, Coolican²⁷⁶ describes his method of placing a tibial bone graft between the adductor muscles from the pubis to the femur. Arthrodesis by a bone graft below the joint is considered more desirable, because a graft in such a position is better able to oppose the greater amount of strain that results from the long axis of the femur and the flexor-adductor muscles. In addition, the graft lies in a healthy bed remote from the seat of infection.

With the patient lying on an abduction frame with a hinged leg bar, a 6 inch (15 cm.) incision is made from the pubic tubercle down the line of the adductor longus muscle. The deep fascia is divided over the interval between this muscle and the gracilis. The line of cleavage is opened between the adductor longus in

276. Coolican, J. H.: Bone Grafting in Tuberculous Hips, *Irish J. M. Sc.*, April 1942, pp. 128-132.

front and the adductor brevis and the adductus magnus behind. The adductor longus is retracted, exposing at the bottom of the wound the deep femoral artery with its first perforating branch and the inner side of the femur. The profunda vessels are displaced, and an oval opening is drilled into the femur after subperiosteal exposure about 2 inches (5 cm.) below the lesser trochanter. The adductor longus tendon is partially or completely divided at its origin, and the body of the pubis is exposed beneath the pubic tubercle. A pit of suitable size is drilled in the bone, and a graft is then cut from the tibia on the affected side. This is securely fitted into place between the femur and the body of the pubis, and the wound is closed without drainage. A plaster spica including the frame is applied and left undisturbed for three months, except for being split and reenforced after eight or ten days for removal of the stitches.

Five case reports are briefly given. In all of these roentgenograms showed that the grafts were united at twelve, thirteen, eight, four and two months after operation.

[ED. NOTE.—Ischiofemoral or pubofemoral arthrodesis is of value in tuberculous hips in which there is an extensive destruction of the ilium as well as of the femoral head and neck. In addition to the procedures mentioned in this paper, that of Bosworth should be noted. All of these operations are technically difficult.]

A new technic for arthrodesis of the elbow for tuberculosis is presented by Nickerson,²⁷⁷ and 3 case histories are reported. The procedure is similar to that of Hallock, in that the graft is taken from the olecranon and the triceps muscle is left attached. Nickerson's method differs in that a U-shaped wedge of bone is taken from the olecranon, so as to leave the medial and lateral portions of the olecranon intact. The proximal end of the graft is inserted into the humerus and the distal end wedged into the "fish" mouth of the olecranon. The triceps tendon is then plicated on itself. Three cases are reported in which fusion was obtained after one operation.

Wassersug²⁷⁸ reviews 46 cases of tuberculosis of the ankle and 42 of the foot in which the patients were treated at the Lakeville State Sanatorium in Massachusetts. Seventeen of the 46 patients with involvement of the ankle died. Eleven of them had some other tuberculous focus. The diagnosis was proved in 40 cases. Three patients who had an arthrodesis performed died. Amputation was necessary in 11 patients who were treated conservatively. In the group with tuberculosis of the foot, 3 died. Two arthrodeses were performed, and there were 7 amputations.

[ED. NOTE.—This is an unusually high percentage of deaths and amputations in a series of patients with involvement of the foot and ankle. Delay in diagnosis and treatment before the patients were received and serious complicating lesions may explain these results. Certainly experience has shown that when an early diagnosis is made and arthrodesis is done cure results in a great majority of cases.]

Cleveland and Bosworth²⁷⁹ give an illuminating report of a study of pathologic material from cases of tuberculosis of the spine from their service at Sea View Hospital, New York.

They found no evidence that tuberculosis begins in the intervertebral disks, but found that it practically always has its inception in the vertebral bodies.

277. Nickerson, S. H.: Modified Approach in Surgery for Tuberculosis of Elbow in Adult. *Am. J. Surg.* 56:483-487 (May) 1942.

278. Wassersug, J. D.: Tuberculosis of Foot and Ankle in Adults and Children. *New England J. Med.* 227:436-439 (Sept. 17) 1942.

279. Cleveland, M., and Bosworth, D. M.: Pathology of Tuberculosis of Spine. *J. Bone & Joint Surg.* 24:527-546 (July) 1942.

In the latter, two processes were found, the first a caseating, destructive lesion, such as usually has been described, and the second a sclerosis of bone associated with necrosis. The latter either had the pattern of an infarct from the occlusion of an artery or was peripheral. The authors conclude that the sclerosis is caused by interruption of the blood supply to the vertebral body by stripping up of the periosteum by an abscess. This may occur over a wide area and may spread for some distance from the original focus. Examination of the spines at autopsy revealed many lesions which were not demonstrated by roentgenograms either of the spine as seen before the patients died or of the specimens taken afterward.

[ED. NOTE.—The frequency of a sclerosing necrosis of bone from deprivation of blood supply in spinal tuberculosis has not been generally appreciated. The finding that the disease does not begin in the intervertebral disk, however, has been generally accepted. One of the earliest roentgenologic findings is thinning of the intervertebral disk, but this is not due to early invasion by disease. It has been the experience of one editor (A. D. S.) also that many tuberculous lesions of the vertebral bodies cannot be detected by the usual roentgenographic examination. Several of these obscure lesions have been successfully demonstrated by means of the laminagraph, and it is advised that this means be employed in doubtful cases when it is available.]

Auerbach²⁸⁰ reports that at Sea View Hospital, in New York, the department of pathology performed in eight and one-half years 95 autopsies for tuberculosis of the thoracic vertebrae and the ribs. Fifteen of these revealed abscesses that had ruptured into the lung. Three abscesses had ruptured into the pleural cavity.

The cause of perforation is enlargement of a paravertebral or costal abscess by increasing amounts of liquefied caseous material. A perifocal reaction occurs in the overlying pleura, producing thickening and firm adhesion to the endothoracic tissue. All fascial planes are thus obliterated, and no further extension of the abscess can occur. As it continues to enlarge, it must progress into the parenchyma of the lung and rupture into the bronchi.

The extension is entirely different when there is perforation into the pleural cavity. Here a tuberculous pleuritis must be present before the perforation occurs, with the tuberculous exudate within the pleural space, keeping the visceral and parietal layers separated.

The symptoms of onset are sudden cough and copious expectoration. The sputum suddenly begins to contain tubercle bacilli. Dense pneumonic shadows appear in previously clear lungs. There is an atypical location of the pulmonary tuberculosis, because it is adjacent to the site of the lesion in the bone. Cold abscesses appear generally in the lower lobe.

A clinical report is made by Monfort and Solomon²⁸¹ of a 16 month old Negro boy who after trauma to the head had a lesion of the skull. The skull and the left humerus roentgenographically exhibited punched-out, circumscribed bone defects described as osteitis tuberculosa multiplex cystoides. Biopsy specimens from the lesions in the skull and in the humerus were histologically characteristic of tuberculosis. Additional clinical diagnoses were mediastinal lymphoglandular tuberculosis, mastoiditis and tuberculosis of the spine.

280. Auerbach, O.: Rupture of Cold Abscesses into Lungs and Pleurae, *Clinics* 1:600-614 (Oct.) 1942.

281. Monfort, J. A., and Solomon, N. H.: Osteitis Tuberculosa Multiplex Cystoides in Children, *Am. J. Dis. Child.* 63:346-353 (Feb.) 1942.

Meng and Wu²⁸² describe 40 cases of adolescents with tuberculosis of the cranium secondary to tuberculosis of the lungs or joints, cold abscesses or sinuses.

[ED. NOTE.—The great prevalence of tuberculosis in China results in the occurrence of many lesions which are rare in this country. Reports of such lesions are interesting and of some value in throwing light on the occasional case seen here.]

A case is reported by Sweet and Abramson²⁸³ of a 3 year old Negro child with bacteriologically proved tuberculous lesions of the left radius, right ulna and left fifth metacarpal bone associated with swelling of the soft parts and formation of sinuses. Roentgenograms of these long bones exhibited periostitis, expansion of shafts and cystlike areas of resorption of medulla and cortex which the authors report as multiple cystic tuberculosis. Criteria are outlined for differentiating this condition from Jüngling's disease.

De Gara²⁸⁴ reports on 195 patients with extrapulmonary tuberculosis examined from 1934 to 1939 in northern Italy. Tubercle bacilli of the bovine type were found in 18, or 9.2 per cent. Of these patients 174 had tuberculous lesions of bones and joints; in 13 (7.4 per cent) the lesions were caused by bacilli of the bovine type. The remaining 21 patients had lesions of the cervical lymph nodes; in 5 of these (23.8 per cent) the lesions were due to organisms of the bovine type.

Bovine tuberculosis was observed in 40 per cent of the affected children less than 5 years of age, in 16.6 per cent of those between the ages of 5 and 15 years, and in 6.4 per cent of the persons older than 15 years.

The importance of infected raw milk or of prolonged contact with infected cattle in the causation of infection with bovine tubercle bacilli is described. Included is a table compiled from the literature on the incidence of the bovine type of tuberculosis of bones and joints in various European countries.

[ED. NOTE.—The marked decrease in the incidence of tuberculosis of the bones and joints with the almost complete elimination of tuberculosis of the cervical lymph nodes coincident with the pasteurization of milk and testing of cattle in the greater part of the United States is further proof of the importance of bovine infection in the causation of osseous lesions in children.]

Biopsy study of regional lymph nodes was made by Webster²⁸⁵ in 15 instances of tuberculous joints. The histologic and cultural methods employed gave consistent results, except in 1 case in which the result of culture was negative. Only the human type of *Mycobacterium tuberculosis* was reported as being found.

Tuberculous lymphadenitis was demonstrated in the inguinal lymphatic nodes in 6 of 7 patients, all but 1 of whom were children, suffering from tuberculosis of the knee joint; in nodes of the same group in 2 of 6 children suspected of tuberculosis of the hip joint; in an inguinal node also of 1 adult patient exhibiting advanced tuberculosis of the ankle joint and in an axillary node of a child with tuberculosis of the wrist joint. Lymphatic drainage of joints is discussed and reasons are suggested against the acceptance of the finding of tuberculosis in lymphatic nodes of the superficial inguinal group as significant of tuberculous disease of the hip joint. In 15 patients with nontuberculous arthritis, biopsy specimens of the regional lymphatic nodes showed no evidence of tuberculosis.

282. Meng, C. M., and Wu, Y. K.: Tuberculosis of Flat Bones of Vault of Skull: Study of Forty Cases, *J. Bone & Joint Surg.* **24**:341-353 (April) 1942.

283. Sweet, L. K., and Abramson, D. J.: Multiple Cystic Tuberculosis of Long Bones, *J. Pediat.* **19**:826-832 (Dec.) 1941.

284. de Gara, P. F.: Bovine Tuberculosis: Its Incidence in Bone, Joint and Cervical Lymph Node Lesions in Italy, *Am. Rev. Tuberc.* **45**:576-585 (May) 1942.

285. Webster, R.: Studies in Tuberculosis: Biopsy Study of Lymphatic Glands in Diagnosis of Tuberculous Disease of Joints, *M. J. Australia* **1**:160-166 (Feb 7) 1942.

Howard, Johnston and Mitchell²⁸⁶ measured the sensitivity to tuberculin in children by using dilutions of old tuberculin and determining thresholds of reaction in 19 patients with tuberculosis of bone. All presented evidence of primary pulmonary infection, the process being active in most cases and healed in several. Nine showed multiple involvement of bones or other tuberculous complications. In 4 children 2 years old the initial threshold reactions at the start of osseous involvement were elicited by 0.1 to 0.01 mg. of old tuberculin. These amounts subsequently fell to 0.0001 to 0.00000001 mg. and then rose again to 0.01 and 0.001 mg. with the healing of the process three to seven years later. A second group of 7 children who did not appear for treatment until after bones were involved had the same rise and fall pattern of allergy. A group of 5 children showed a high plateau of sensitivity for from three to six years, associated with poor ability to heal. There was 1 death from constantly spreading tuberculous infection. On the basis of this series, which the authors admit is small, it is concluded that a rise to a high level of sensitivity with a subsequent fall is characteristic of the evolution of the healing process in osseous tuberculosis, and that sustained high levels of allergy have characterized lesions which have shown a failure to heal.

X. INFECTIONS OF BONES AND JOINTS EXCLUSIVE OF TUBERCULOSIS

PREPARED BY PAUL C. COLONNA, M.D., PHILADELPHIA

ASSISTED BY E. B. DUNLOP, M.D., DAVID J. KING, M.D., AND THOMAS GUCKER, III, M.D.

General Considerations.—Mahorner and Crain²⁸⁷ review 178 cases of acute hematogenous osteomyelitis: Sixty-six patients were treated in the years 1937 to 1940, with a mortality of 6.6 per cent, and 112 in the years 1930 to 1936, with a mortality of 24 per cent. Treatment was carried out as follows:

1. Hydration and replacement of electrolytes were achieved by administration of dextrose and isotonic solution of sodium chloride.

2. Protein replacement with repeated transfusions.

3. Oral chemotherapy with daily doses of 0.2 Gm. of sulfathiazole per kilogram of body weight or intravenous chemotherapy with amounts of a 5 per cent solution sufficient to provide 0.06 Gm. per kilogram of the drug in twenty-four hours had definite value. The rationality of the type of chemotherapy employed was verified by cultures.

4. Immunotherapy with staphylococcus antitoxin and staphylococcus toxoid is a recent development.

5. After the patient had been prepared by the foregoing measures and the disease had endured long enough for pus to form, incision and drainage or osteotomy was done and petrolatum gauze packing inserted. Early emergency operation may convert periostitis into osteomyelitis. Ligation of veins is indicated if cultures of the blood remain positive and sequestrectomy should be done if there is continuation of drainage and inflammatory reaction with or without roentgen evidence.

6. Immobilization by means of traction or a plaster cast is important and may in some cases be solely responsible for a drop in temperature when other methods are ineffectual.

286. Howard, P. J.; Johnston, J. A., and Mitchell, C. L.: Tuberculin Sensitivity in Children with Bone Tuberculosis, *Am. Rev. Tuberc.* **46**:532-545 (Nov.) 1942.

287. Mahorner, H., and Crain, A. P., Jr.: Acute Hematogenous Osteomyelitis, *Ann. Surg.* **115**:790-815 (May) 1942.

Follow-up of 42 of the 66 patients in the 1937 to 1940 series revealed that in 20 (47.6 per cent) the infection had healed in an average time of seventeen months. Fourteen had been subjected to osteotomy and 7 to incision and drainage, and 1 had not been operated on. Thirty-four patients wore plaster encasements for an average of eleven months. Of the 13 patients who were given sulfathiazole, 8 had staphylococcus bacteremia and 4 wounds from which staphylococci could be cultured. Six patients were given staphylococcus antitoxin. The authors conclude that ligation of veins is a safe adjunct to treatment, though its effectiveness has not yet been proved.

This article emphasizes the fact that since osteomyelitis is a vascular or intravascular disease venous ligation constitutes reasonable treatment. Recent studies on the pathogenesis of osteomyelitis suggest that it begins under the periosteum or in the cortex of the bone and causes osseous cellulitis.

[ED. NOTE.—The authors are optimistic to call the infection healed after a short follow-up period.]

Buchman²⁸⁸ discusses three forms of osteomyelitis:

1. Acute osteomyelitis: In explaining its pathogenesis he mentions a theory of localization based on the fact that phagocytosis is less in the metaphysis than in the diaphysis. He stresses the importance of the invasiveness of bacteria, rather than their toxigenicity, in the production of osteomyelitis and also speaks of a "spreading factor" described by Duran-Reynals which increases the permeability of the tissues to bacteria. He suggests variations in treatment for each of four types of acute osteomyelitis: (1) fulminating, (2) severe acute, (3) ordinary acute and (4) mild. General treatment should include rest, blood transfusions and administration of fluids. Immunotransfusions to overcome bacteremia and antitoxins to combat toxemia are also helpful. Local treatment consists of prompt, efficient and conservative surgical drainage of metaphysis followed by packing with petrolatum gauze and immobilization in a circular plaster of Paris bandage for four to six weeks. For infants under 2 years and for the fulminating and severe acute types of the disease, he advises primary consideration of systemic invasiveness and toxemia, operative intervention being delayed until the former is under control and definite evidence of a local osseous lesion is present.

2. Postacute osteomyelitis: Here there is a slow downhill course with persistent draining sinuses, pathologic fractures and deformities. General treatment includes a diet of high caloric value and rich in vitamins. Secondary anemia is treated with hematinics, liver extracts and transfusions. Local treatment consists of thorough drainage and the use of plaster supports.

3. Chronic osteomyelitis: This is characterized by local lesions intermittently healing and becoming reactivated. It is treated by excision of diseased tissue as radically as possible, saucerized wound being lined with petrolatum gauze and the cavity packed with dry gauze. A huge compression bandage is then applied. Plaster is used only when a pathologic fracture is anticipated. A week to ten days later the packing is removed, sterile maggots are implanted and the wound is covered with a single layer of fine-meshed cheesecloth held in place by liquid adhesive. Maggots are replaced as soon as they die, and renewal is continued as long as necessary. The author believes that allantoin, urea and maggot substitutes are much less effective because they "lack the stimulus to rapid formation of granulations resulting from the subminimal physical irritation incidental to the continuous crawling about of the maggots."

288. Buchman, J.: Osteomyelitis, in Litchfield, H. R., and Dembo, L. H.: *Therapeutics of Infancy and Childhood*, Philadelphia, F. A. Davis Company, 1942, vol. 4, p. 3732.

The author raises the question of how to treat lesions which appear clinically to be new but which roentgenograms reveal to be chronic. He concludes that in the acute phase sulfonamide compounds are beneficial only to overcome bacteremia and do not significantly influence either primary or secondary foci and that in the chronic stage they are even less valuable. He mentions Dickson, Diveley and Kiene's method of preoperative and postoperative oral administration of sulfa-thiazole combined with topical application of the drug to the saucerized wound, which is closed without drainage. He feels, however, that this method is still in the experimental stage.

[ED. NOTE.—There is insufficient emphasis on immobilization in plaster, both in the acute and in the chronic stage. The author is somewhat too pessimistic about therapy with sulfonamide compounds.]

Brailsford,²⁸⁹ in discussing chronic abscesses of bone, states that the clinical features are attacks of pain in the affected extremity, which may be mild or severe and are initiated by jarring. There may be no local signs of inflammation and no changes in the subcutaneous tissue, and the patient may be afebrile. Local swelling may be noted if the involved part of the bone is near the skin. Trauma appears to be a causative influence. The lesions seem to be more frequent between the ages of 10 and 20. Clinically it may have to be differentiated from a neurologic condition (herniated intravertebral disk).

The roentgenogram generally shows a spindle-shaped accretion of new periosteal bone with a central translucent area on a plane with the original periosteum. The new bone at first is less dense than the normal cortex, and the latter becomes absorbed into new bone. There is no clear demarcation at the boundary between new and normal bone.

The treatment consists of a localized resection of the cortex, including the central focus. On section the tissue appears like osteoid osteoma, which in its early stages shows a large amount of osteoid tissue, later becoming calcified. Hence from the roentgen appearance it may be mislabeled chronic sclerosing, non-suppurative osteomyelitis, intracortical abscess, syphilitic osteoperiostitis, sclerosing osteogenic sarcoma or osteochondritis dissecans.

[ED. NOTE.—The author has made no mention of antecedent or coincidental cutaneous infections, and in 4 cases diagnosis was not confirmed by operation, since none was performed.]

Maxfield and Mitchell²⁹⁰ report 5 cases of acute osteomyelitis in the adult and stress the point that it has so many characteristic clinical manifestations that it should be considered a separate clinical entity. *Staphylococcus aureus* is usually the organism found, but in 1 of their cases, which was fatal, hemolytic streptococci were noted. In 2 cases the disease was localized in the femoral shaft and was accompanied by pathologic fractures. These authors stress the fact that the onset of the disease is a matter of weeks or even months, that the pain is vague and that the pathologic changes are most apt to center near the middle of the diaphysis. An early manifestation is a light periosteal reaction, and they believe that there are two distinct pathologic types, one characterized by primary periosteal involvement with secondary invasion of the medullary shaft and the other by a low grade infection of the central area with secondary spread to the periosteum. In the latter type, with one or more central areas of rarefaction, the condition may be interpreted

289. Brailsford, J. F.: Chronic Sub-Periosteal Abscess, *Brit. J. Radiol.* **15**:313-317 (Nov.) 1942.

290. Maxfield, E., and Mitchell, C.: Acute Hematogenous Osteomyelitis in Adult, *J. Bone & Joint Surg.* **24**:647-652 (July) 1942.

as an abscess of bone if only a casual examination is made, but the authors point out that the abscess does not show a light periosteal reaction but there is an area of sclerosis around its margin. In addition it differs from the adult form of acute osteomyelitis in that it is characteristically near the epiphysis rather than in the center of the diaphysis. The treatment consists of adequate drainage.

[ED. NOTE.—The diagnosis of this disease may be extremely difficult, particularly when the infection is in the central area primarily. For this reason early exploration may prevent the process from going on to pathologic fracture. Wide saucerization followed by the Orr method of treatment is advocated.]

Meyerding and Clegg,²⁹¹ after reviewing the pathology and clinical picture of osteomyelitis, stress the value of the use of sulfanilamide and sulfathiazole. They point out that the marked similarity of Ewing's tumor and osteomyelitis, as revealed by the symptoms and roentgenographic findings, cannot be overemphasized. In discussing acute osteomyelitis they state, surprisingly: "Although most authors still advocate immediate incision and drainage and the instillation of petrolatum packs (Orr's method of treatment) or the use of dakinization, some believe that incision of periosteum and soft tissue abscess is preferable." The authors feel that the sulfonamide compounds are especially effective in cases in which septicemia is a complicating factor and recommend sufficient amounts of these drugs to maintain a concentration of 10 mg. per hundred cubic centimeters of blood. The local administration of 10 to 15 Gm. of the powdered drug is indicated as an adjunct in the treatment of open wounds. They contend that the drug should be injected into sinuses or cavities when mixed with cod liver oil—5 Gm. of either drug with 30 cc. of oil. Although they realize that there may be certain individual hypersensitivities to chemotherapy, they have not encountered any serious damage from the use of either of these drugs.

A report is then made of 8 illustrative cases showing the occasional difficulty of differentiating osteomyelitis from Ewing's tumor and demonstrating the chronic persistence of osteomyelitis for twenty-six years. The authors mention the possibility that malignant disease may develop in infections associated with long drainage. Several other cases illustrative of the value of adequate chemotherapy are reported. The authors believe that the drug should be taken both orally and locally in all cases of osteomyelitis and septicemia. When the drug is taken before localization of the disease in the bones adequate chemotherapy may prevent osteomyelitis and its complications. The authors feel that when large abscesses have formed adequate surgical drainage of the infected region should still be done.

[ED. NOTE.—The bacteriostatic action of the sulfonamide compounds plus adequate surgical treatment in osteomyelitis, whether of streptococcic or staphylococcic origin, has paved the way for the development of many other drugs. The authors' statement regarding the widespread use of the Orr treatment in acute osteomyelitis is not accepted by the editors. The recent report on penicillin would seem to indicate that in this drug one has an even more potent substance for combating the *Staphylococcus aureus*.]

In an article designed to evaluate the present methods of treatment of chronic osteomyelitis (namely, treatment by the Carrel-Dakin and the Orr method, treatment with "bipp" and treatment with maggots), Buchman²⁹² reviews briefly the history of the treatment of this condition, its pathology, the "basic surgical attack"

291. Meyerding, H. W., and Clegg, R. S.: Modern Treatment of Osteomyelitis, *Am. J. Surg.* 57:56-64 (July) 1942.

292. Buchman, J.: Treatment of Chronic Osteomyelitis, *S. Clin. North America* 22:581-595 (April) 1942.

(tourniquet control, a liberal incision, stripping of the periosteum within the limits of incision, saucerization from normal bone above to normal bone below, removal of all visible foci and overhanging shelves, thorough cleansing with hot isotonic solution of sodium chloride to remove debris and to control oozing, and immobilization of the part), and the problem of closure of the wound. (The author stresses the importance of the time factor involved in the formation of healthy granulation tissue, which should proliferate with sufficient rapidity to fill the entire cavity before the blood supply is damaged by the forming fibrous tissue.)

With the foregoing considerations in mind, Buchman established the following criteria for successful treatment:

1. Thorough surgical removal of all diseased and scarred tissue, and removal of all foreign bodies.
2. Efficient removal of wound discharges.
3. Efficient and harmless disinfection of the wound.
4. Even and rapid filling of the wound with healthy granulation tissue before circulation has become impaired.

The Carrel-Dakin method fulfils only the first two of the above prerequisites; the Orr method fulfils the first, second and third, but the author recognizes it as effective under war conditions; treatment with "bipp" (bismuth subnitrate, iodoform and petrolatum paste) is similar in effectiveness to the Orr method; treatment with maggots fulfils all of the criteria listed by the author, who strongly favors this method for handling selected cases.

The importance of not overlooking the systemic aspects of osteomyelitis is brought out. The diet should be of high caloric value and rich in vitamins, and proper hygienic care should be insisted on. In the presence of secondary anemia, hematinics, liver therapy and transfusions may be indicated.

[ED. NOTE.—This is an excellent résumé of the subject, though the editors feel that the disadvantages of the use of maggots have not been sufficiently stressed in this article.]

Traumatic Wounds.—Livingston²⁹³ reports a study of 22,954 fractures of long bones received in battle. Eighty per cent of these battle fractures were compound, and about one half of the compound fractures required over five years to become stationary. He believes that mobile hospitals should be equipped so that a major surgical operation can be performed within seventy-two hours after injury. In 1930 there were 10,000 cases of old and recent osteomyelitis in the Veterans Administration.

The author reached the following conclusions:

1. Compound fractures should have early anatomic alinement by open or closed manipulation and should be maintained by internal or external fixation. Hardware can be used at the time of débridement and infection does not contraindicate its use.
2. Thorough, careful débridement is advisable.
3. Antitetanus and anti-gas-gangrene serums should be given prophylactically in all cases and should be repeated before delayed operation is attempted.
4. Shock should be treated by intravenously injected serum or plasma.

293. Livingston, S. K.: Results in Compound Fractures with Osteomyelitis as Experienced by Veterans Administration over Past Twenty Years, *Surg., Gynec. & Obst.* **74**:546-548 (Feb., no. 2 A) 1942.

5. Both oral and local treatment with sulfonamide compounds are recommended.
6. Sequestrectomy in chronic osteomyelitis should be thorough and should include areas of osteosclerosis. Progressing molecular necrosis requires either amputation or wide excision to areas obtaining their blood supply from the collateral circulation.
7. Symes and Gritti-Stokes amputations are those of election. Amputation at the calf should usually be avoided.
8. Treatment with maggots and treatment by the Orr method are both effective for osteomyelitis.
9. Local irrigating solutions, antiseptics and pastes are not effective in the treatment of osteomyelitis.

Caldwell²⁹⁴ divides traumatic lesions into abrasions and incised, punctured, lacerated, contused and gunshot wounds and states that the organisms usually found are the staphylococcus, the streptococcus and the anaerobes producing tetanus and gas gangrene. He stresses the fact that the only effective treatment of post-traumatic infections is preventive. Stressing the benefit of the sulfonamide compounds both orally and intravenously, he cites experimental work showing that immediate implantation of the sulfonamide derivatives at the time of the accident followed by an adequate surgical procedure and reimplantation of the drug locally is most effective in preventing all infections.

The ideal plan he outlines would consist of immediate implantation in the wound of 5 to 20 Gm. of sulfathiazole, use of transportation splints and appropriate shock treatment, thorough débridement within six hours of injury, with reimplantation of sulfathiazole, primary closure of the wound, unless more than six hours has elapsed, and intravenous or oral administration of sulfathiazole for five to seven days postoperatively. Tetanus antitoxin and combined tetanus and polyvalent gas gangrene antitoxin should be administered routinely to all patients with incised, lacerated or punctured wounds.

[ED. NOTE.—This is an excellent summary of the treatment of infection developing after trauma to the extremities.]

Types of Osteomyelitis.—To illustrate the confusion in the diagnosis of osseous syphilis, Alexander and Schoch²⁹⁵ present 2 cases in which the clinical manifestations were unusual and difficult of explanation. Because of the negative serologic report, confusion arose, and in 1 case diagnosis was greatly delayed, while in the other tuberculosis was considered the most likely diagnosis. In each of these cases the patient responded dramatically to antisiphilic therapy. The authors make the pertinent comment that if syphilis is even suspected a trial of antisiphilic treatment is advisable before more radical measures are attempted.

[ED. NOTE.—One is constantly being reminded of the multiplicity of lesions attributable to the ubiquitous *Treponema pallidum*.]

Rosenberg, Dockerty and Meyerding²⁹⁶ state that of 514 cases of coccidioidal granuloma reported up to April 1941, with 249 deaths, approximately 90 per cent

294. Caldwell, G. A.: War Surgery and Traumatic Lesions: Post-Traumatic Infections of Extremities, *Am. J. Surg.* **56**:64-69 (April) 1942.

295. Alexander, L. J., and Schoch, A. G.: Osseous Syphilis: Confusion in Diagnosis; Report of Two Cases of Osteomyelitis of Late Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:397-406 (July) 1942.

296. Rosenberg, F.; Dockerty, M. B., and Meyerding, H. W.: Coccidioidal Arthritis: Report of Case in Which Ankles Were Involved and Condition Was Unaffected by Sulfanilamide and Roentgen Therapy, *Arch. Int. Med.* **69**:238-250 (Feb.) 1942; correction, *ibid.* **69**:717 (April) 1942.

were in patients observed in California and 66 per cent have been reported from the central and southern sections of the state.

Until recently, the fungus *Coccidioides immitis* was thought to cause only one type of disease, a chronic granulomatous infection with clinical and pathologic features similar to those of tuberculosis and known to affect the skin, the lymph nodes, the abdominal and thoracic viscera, the meninges and the bones and joints. Endemic in the Sacramento-San Joaquin Valley area for fifty years had been a disease known locally as "valley fever," "desert fever," "desert rheumatism," "San Joaquin Valley fever" or "the bumps" and characterized by acute onset of malaise, general aches and pains, "toxic erythema," sore throat with fever, and occasionally conjunctivitis and signs of bronchopneumonia. Eight to fifteen days after onset, when improvement of the aforementioned symptoms is noticed, lesions typical of erythema nodosum appear, mainly on the skin. Roentgenograms of the chest at that stage of the disease disclose the presence of opaque areas suggestive of tuberculosis. Until 1936 the cause of this disease remained unknown. At that time Dickson and Smith found that the fungus *C. immitis* could be obtained from sputum of patients and that positive subcutaneous injection of test doses of a broth filtrate (coccidioidin) could be made.

There are two phases in the life cycle of *C. immitis*. During the vegetative phase, the fungus lives in soil and vegetation, and during the parasitic phase it inhabits the body of the infected host. The modes of entry are inhalation, direct contact with abrasions of the skin and "inoculation infection."

Involvement of joints occurs both in the acute benign phase and the chronic granulomatous phase of coccidioidal infection. Acute arthritis develops in about one third of the patients with "valley fever," usually appearing simultaneously with erythema nodosum and always clearing without residual damage or deformity. Treatment consists of rest in bed, symptomatic relief by administration of salicylates, etc.

Lesions of bones and joints are fairly common in the chronic granulomatous stage of the disease. Arthritis, often multiple, was present in 79 of 256 cases reported in 1931. Early the joints are swollen and red; later fluctuation may appear. Nodular lesions may develop in skin overlying the affected joints and may ulcerate and discharge pus containing *C. immitis*. Roentgen changes may mimic those of tuberculous arthritis, with destruction of cartilage and narrowing of joint spaces. There is little tendency toward production of bone in early lesions of the chronic form of the disease. The authors point out that whereas tuberculosis often attacks the joints directly, coccidioidal granuloma does so by extension from adjacent osseous lesions and that the latter more often affect multiple joints. This disease should be suspected in residents of or visitors in local endemic areas complaining of chronic progressive arthritis and in the presence of evidence of rapid progress of a destructive process in bone. No therapy has been of specific value for the chronic phase of this disease. Studies thus far reveal that sulfanilamide is not effective against this fungus.

An excellent article on the coccidioidal infections of bone by Benninghoven and Miller²⁹⁷ reviews the subject of coccidioidal infection, about 500 cases of which have been reported to the California State Department of Health during the last forty years.

The disease is produced by the fungus *Oidium coccidioides*, which is usually found in the soil, and the adult form contains endospores which produce nodules

297. Benninghoven, D., and Miller, E. R.: Coccidioidal Infection in Bone, *Radiology* **38**: 663-666 (June) 1942.

closely resembling those of tuberculosis. Males are affected four times as frequently as females, probably because persons engaged in ranching and fruit picking, in which contact with the soil is close, are most frequently affected. The cases usually originate in the middle and southern parts of California. The portal of entry is the respiratory tract, the patient clinically having a mild influenza which may or may not be associated with erythema nodosum. In this primary phase a roentgenogram of the chest shows a small pneumonic focus with adenopathy resembling that of the primary phase of tuberculosis. In this phase the patient has a positive cutaneous allergic response to coccidioidin. All patients recover from the primary infection within a few weeks. Reinfection may induce the disease in its secondary or chronic granulomatous phase. Fortunately the secondary phase develops in only a small percentage of the patients. After the secondary focus is established either in the lungs or in the skin, metastatic foci may appear in the soft tissues, bones or parenchymal organs, and miliary dissemination is the terminal manifestation, dissemination being by the blood and lymph streams.

There are several commonly encountered types of osseous lesions found in this disease which may closely resemble tuberculosis of the bones or joints. Unilocular and multilocular cystlike areas, marginal erosions and destructive lesions with periosteal formation of new bone and abscesses of the soft tissues may develop. These lesions may go on to an advanced stage, giving rise to destruction with periosteal formation of new bone surrounding infected soft tissue, but sequestration, either with or without articular involvement, is rare. There is another type frequently seen in the short bones of the hand or feet or even in the shaft of a long bone showing widespread destruction. The articular involvement may be of two distinctly different types—the purely synovial or the synovial with subarticular destruction, which is indistinguishable from tuberculosis. Here there are capsular swelling and extensive periarticular osteoporosis, with cartilage and subarticular destruction of bone on both sides of the joint.

A multiplicity of lesions is the rule, and the bones most frequently involved are those of the spine, pelvis, hands and feet and the bones adjacent to the knee and ankle. No bones are exempt, though the diaphysial lesions are rare except in the short bones of the hands and feet. Coccidioidosis frequently may be indistinguishable clinically and roentgenographically from Pott's disease. The epiphysial cartilage, however, does not act as a barrier to the spread of the infection. Synovial infection may remain limited entirely to the synovium. Abscesses of the soft tissues are common. They may arise as primary lesions without involvement of bone, or they may extend to the underlying bone and involve it.

The prognosis of this disease in the secondary phase is grave, and the authors state that there is a mortality of approximately 60 per cent.

[ED. NOTE.—These excellent papers on a disease whose secondary phase may so closely resemble tuberculosis are of extreme practical interest. While most cases seem to originate in the middle and southern parts of California, any condition that so closely resembles osseous tuberculosis must be watched for in other localities. The multiplicity of lesions so frequently found and the high mortality are, however, somewhat different from the manifestations of the infections with acid-fast organisms.]

Gajzágó and Göttche²⁹⁸ describe 6 cases of infections with *Salmonella suipestifer* in children. Human infection with *S. suipestifer* was observed first during World

298. Gajzágó, D., and Göttche, O.: Suipestifer-Infektionen im Kindesalter, *Monatschr. f. Kinderh.* 88:166-185, 1941; *Salmonella Suipestifer Infections in Childhood*, *Am. J. Dis. Child.* 63:15-29 (Jan.) 1942.

War I, when it occurred in epidemic form. Subsequently infections attributed to food (raw milk, puddings, ice cream) were reported. The clinical picture resembled that of typhoid or dysentery. Later also sporadic cases were reported, and it was noted that the infection might appear in manifold forms such as pneumonia, pyelocystitis, cholecystitis, meningitis and endopericarditis, as well as in the forms resembling typhoid and dysentery. *S. suispestifer* has been isolated from abscesses of the liver, abscesses in uterine myoma and pyosalpinx.

In adults the condition is serious. In 19 of the 31 sporadic cases in which it has occurred in adults it has been fatal, but possibly the milder forms of the disease have not been recognized. In all, 28 cases of this infection in children have been reported. Fourteen cases have been reported in the United States, 10 of which were from Baltimore. The disease is more benign in children, the mortality rate being only 6 per cent. In 17 of 34 cases the organism caused an osteomyelitis. All osseous lesions were in infants under 2 years of age. In children over 2 years of age osteomyelitis did not occur. All of the 6 infants reported on by the present writers showed osteomyelitis.

Clinically, roentgenologically and pathologically this type of osteomyelitis is relatively benign. Incision was necessary in only 1 case. There may be multiple osseous foci and recurrences. The internal organs are not involved, and there is no anemia. The roentgen changes are very slight and become manifest in the fourth to the sixth week. Most of the foci appear in the proximal metaphysis of the humerus, i. e. in the shoulder region, or in the distal metaphysis of the femur, i. e. in the knee region. Slight inflammatory symptoms in these regions should rouse suspicion of infection with *S. suispestifer*. When suppuration is present, the organism can be isolated from the pus. The agglutination test gave a positive result in considerable dilution in all cases. In 2 of the 34 cases other organisms besides *S. suispestifer* were present. Most of the children were from poor country districts. In 1 case a hog dealer who had lost several hogs from infection lived in the house. Since some of the children were breast fed, it seems hardly possible that they had become infected from the hogs. The organism exists in the intestine of 10 per cent of normal swine. It seems probable that in epidemics of infection from food the latter was infected by food handlers, as carriers have been detected. The lower resistance of infants renders them susceptible to infection which does not attack their parents or the older children in the family. The infection is much more common than is supposed.

Localization of Infections.—Garlock²⁹⁹ reports that in a previous series of 42 infections of tendon sheaths of the hand, only 14 per cent of the patients had restoration of normal function. He concludes that three factors determine the results: (1) the duration of the disease before treatment (if it is over twenty-four hours there is little chance of survival of the involved tendons); (2) the degree of tension within the sheath, with its direct influence on the precarious blood supply to the tendons; (3) the introduction of secondary contaminant organisms after open drainage of the flexor sheaths, causing necrosis; (4) the virulence of the infecting organism and the resistance of the host.

On these premises he advises the following treatment: 1. If the infection is of less than twenty-four hours' duration, aspirate the tendon sheath as completely as possible. 2. Make smears and cultures of the aspirated material. 3. Administer sulfonamide compounds at once—preferably intravenously. 4. If there are only moderate tension and swelling in the sheath, immobilize the digit in partial flexion

299. Garlock, J. H.: Suppurative Tenosynovitis of Hand: Plan of Treatment, *J. Mt. Sinai Hosp.* 8:540-542 (Jan.-Feb.) 1942.

and use hot soaks if desired. 5. If there are great tension and swelling, make lateral incisions in a bloodless field, with multiple small incisions in the tendon sheath. Do not use a drain. 6. Apply a light dressing and immobilize the finger in partial flexion with a sterile metal splint. Wrap the hand and forearm in sterile towels. Leave the dressings on for three or four days and continue treatment with a sulfonamide compound. 7. Start early active motion. The author reports 5 cases in which the patients were treated by this method. In 4 cases hemolytic streptococci were the infecting organisms, and in 1 case it was *Staphylococcus aureus*. The fingers infected with streptococci were all restored to complete function. The patient with staphylococcic infection had a serviceable digit with slight limitation of flexion.

Chont³⁰⁰ points out that the commonest causative agents of suppurative arthritis of the hip in children under the age of 2 are the streptococcus and the meningococcus. In older children the offending organism is usually the staphylococcus. The gonococcus may be the causative agent at any age.

Since the infection is blood borne, there are symptoms of toxemia. Local signs are pain, swelling and impaired function of the hip. These signs and symptoms occur also with periarthritis, toxic reaction of the joint, nonpurulent synovitis and osteomyelitis. Roentgen examination helps to differentiate suppurative arthritis of the hip from osteomyelitis.

Suppurative arthritis of the hip begins with an increased secretion of serum into the joint cavity, which produces an increased intracapsular pressure. A lateral and upward subluxation or dislocation of the head of the femur occurs. Later the synovial fluid becomes purulent and destroys cartilage, so that fusion or pathologic dislocation results. This lateral and upward displacement of the head of the femur as demonstrated by the roentgenogram is pathognomonic of early infectious arthritis of the infantile hip. Cases are reported to demonstrate this condition.

Aranow and Wood³⁰¹ review the causes of scarlet fever and point out that different strains of beta hemolytic streptococci may produce antigenically different toxins which cause scarlet fever, but are not neutralized by the standard Dick antitoxin. The purpose of the paper is to report a case with immunologic experiments which suggests that scarlet fever may be caused by staphylococcus toxin.

The case is that of a 15 year old girl who was admitted to the hospital with a history of pain in the left thigh and fever for four days. She was acutely ill, with a temperature of 105 F., and had the typical manifestations of scarlet fever (rash, glossitis, etc.), associated with tenderness over the lateral aspect of the thigh.

Repeated cultures of the blood showed a hemolytic strain of *Staph. aureus*. Rash and fever responded to scarlet fever antitoxin. Pain and tenderness became localized over the greater trochanter. It was incised and drilled, and pus containing hemolytic *Staph. aureus* was encountered. Treatment with sulfadiazine resulted in continued improvement.

Repeated search revealed no evidence of beta hemolytic streptococci in this case. Experiments carried out on the strain of hemolytic *Staph. aureus* found in the pus showed that filtrable erythrogenic toxin was produced. This toxin was neutralized by commercial scarlatinal antitoxin.

300. Chont, L. K.: Roentgen Sign of Early Suppurative Arthritis of Hip in Infancy, *Radiology* **38**:708-714 (June) 1942.

301. Aranow, H., Jr., and Wood, W. B., Jr.: Staphylococcic Infection Simulating Scarlet Fever, *J. A. M. A.* **119**:1491-1495 (Aug. 29) 1942.

Schein³⁰² reports an unusual complication following the plating of a fractured femur with a long vanadium steel plate. About six months after the plate was applied the patient had a sudden attack of severe pain in the right thigh, without any history of preceding injury or illness, and his temperature rose to 105 F. The wound was opened widely, and the discolored Lane plate was exposed and removed. The plate had become very loose and was bathed in greenish gray pus, from which *Salmonella typhimurium* was cultured. The wound was treated by the Orr method and finally healed without further infection of the bone. The author is convinced that the infection was not a primary osteomyelitis but that it originated from the material that had accumulated about the plate and screws.

The author states that at the Mount Sinai Hospital plates are usually left in situ but that it has been found necessary to remove more than 5 per cent from their plated fractures when the older type of Sherman vanadium steel plate was used.

[ED. NOTE.—The isolation of one of the paratyphoid group of organisms, as well as the fortunate outcome of the case presented, is of interest.]

Goldenberg³⁰³ reports the case of an 11 year old boy whose illness was misdiagnosed as cellulitis of the left leg on the fifth day and later was proved to be osteomyelitis of the fibula. He was given expectant treatment entirely (i. e. dextrose in saline solution intravenously and hot, wet magnesium sulfate dressings), and sulfonamide compounds were not used. On the twelfth day the leg was immobilized in a circular plaster bandage. Support was continued for a period of eight months, during the latter part of which weight bearing was permitted. Periodic roentgenograms showed progressive destruction of the proximal 4 inches (10 cm.) of the fibula with subsequent reformation of the shaft, beginning in the distal part. Three years and two months later there was no roentgen evidence of active disease or sequestrum formation, and complete regeneration of the fibula had taken place.

[ED. NOTE.—The clinical aspects are minimized in this report, and no mention is made of an etiologic agent. It is not recorded whether blood cultures and other laboratory studies were made, though they would be of interest.]

Guthrie³⁰⁴ describes the case of a 7 month old boy with initial symptoms of an infection of the upper respiratory tract followed by arthritis of the right shoulder. Bronchopneumonia developed followed by nuchal rigidity. A lumbar puncture showed slight increase of pressure but otherwise revealed nothing. Autopsy disclosed suppurative periartthritis of the right shoulder without involvement of the joint, pus in the bronchioles, patchy bronchopneumonia of the suppurative type and bilateral otitis media. There was no evidence of meningitis. Bacteriologic, serologic and biologic studies identified the infecting organism as *S. suipestifer*, var. *Kunzendorf*.

In reviewing the literature he found that *Salmonella* infections in early childhood tend to produce bacteremia and foci of suppuration in organs and tissues. *S. suipestifer* may produce lesions in bones and joints, and in 20 per cent of 71 cases of this infection involving the skeletal system septic arthritis was the predominant lesion. Pulmonary complications frequently accompany lesions elsewhere. The

302. Schein, A. J.: Late Infection of Healed Lane-Plated Fracture of Femur by *Salmonella Typhimurium*: Lane Plate as Locus Minoris Resistentiae, *J. Mt. Sinai Hosp.* **9**:154-159 (Sept.-Oct.) 1942.

303. Goldenberg, R. R.: Roentgenographic Study of Acute Osteomyelitis of Fibula Treated Conservatively, *J. Bone & Joint Surg.* **24**:447-451 (April) 1942.

304. Guthrie, K. J.: Suppurative Periartthritis in Infant Due to *Suipestifer Bacillus*, *Arch. Dis. Childhood* **16**:269-274 (Dec.) 1941.

portal of entry is probably the gastrointestinal tract, but pathologic changes are not usually found there and the organism can rarely be isolated from feces. Blood cultures are often positive. The organism can also enter via the rhinopharyngeal portal. Infection by the latter route accounts for the aural and pulmonic involvement in the case cited.

[ED. NOTE.—The author makes no mention of treatment.]

Kirby-Smith³⁰⁵ reports 1 case of osteomyelitis of the patella and states that he has found only 60 reported in the literature. In his case the infection was treated by excising a portion of the patella and draining the wound. When last seen about two years after operation, the patient presented approximately normal return of active function to the joint, and the roentgenograms taken at intervals showed that about ten and a half months after operation the patella had regenerated, although it was rather irregular in outline.

According to McMaster,³⁰⁶ typhoid spine is a rare complication of generalized typhoid infection. In one series of 410 patients only 1 had spinal involvement. The diagnosis of typhoid spine is usually based on the history plus a Widal test. A negative result of the test, however, does not exclude this disease. The physical manifestations include tenderness, muscular spasm, limitation of motion and occasionally scoliosis and kyphosis. By roentgen examination the process can usually be localized to two vertebrae in the lower thoracic or lumbar region. There is narrowing or absence of the intervertebral disks with osteitis of the adjacent vertebral bodies, which themselves may be only slightly invaded. Ossification of the periosteal and perispinal ligaments may produce bridging. Abscesses are rare. In making the differential diagnosis coccidioidal granuloma and brucella spondylitis should be considered. Typhoid organisms may be found in the vertebral marrow many years after generalized infection. The treatment consists of immobilization by means of a plaster cast or a brace. A spinal fusion is indicated if the patient has recurrent attacks of pain in the back with prolonged disability, unless there are serious systemic lesions present.

The author reports 4 cases, in 3 of which the disease was diagnosed five or more years after subsidence of the acute infection. In 2 cases spinal fusion was performed with apparent cure.

Stone³⁰⁷ reviews the literature on osteomyelitis of the long bones in the newborn and reports 4 new cases. He concludes that the disease is relatively benign, with a favorable prognosis. In 63 per cent of the infants in one series the etiologic agent was a streptococcus. In those under 6 months of age the mortality was 44 per cent. When recovery takes place the wounds heal rapidly after drainage, sequestration is rare and recurrences are extremely infrequent. Often a study of end results reveals that the site of the original lesion is roentgenographically invisible. The involucrum is visible much sooner than in older children and usually involves one-half the length of the bone. If the infant survives the acute phase, the disease is of relatively short duration and the prognosis of the osseous lesion is excellent. A minimal amount of surgical intervention is adequate. Drainage is necessary only if there is a palpable mass, and the bone should be left untouched if a secondary abscess can be adequately drained. When the Orr technic was used in treatment healing usually occurred in four to eight weeks.

305. Kirby-Smith, H. T.: Acute Osteomyelitis of Patella: Case Report, *J. Bone & Joint Surg.* **24**:942-944 (Oct.) 1942.

306. McMaster, P. E.: Typhoid Spine, *U. S. Nav. M. Bull.* **40**:957-963 (Oct.) 1942.

307. Stone, S.: Osteomyelitis of Long Bones in Newborn, *Am. J. Dis. Child.* **64**:680-688 (Oct.) 1942.

When osteomyelitis is associated with septicemia or secondary to umbilical sepsis, the prognosis is more grave. Sepsis, not osteomyelitis, kills.

The author reports on 4 cases of osteomyelitis involving long bones. In 1 the infecting organism was *Streptococcus viridans*, and in 3 it was *Staphylococcus aureus*. All the patients recovered, and none had septicemia or appeared acutely ill. They were admitted to the hospital because of localized swellings of the extremities or diminished motion of the arms and legs.

He explains the benign nature of the disease on the basis of the anatomy of the bone of the newborn, which has large vascular spaces and is less rigid than that of adults. The cortical bone is thin, especially at the metaphysis, so that there is freer communication between the marrow and the subperiosteal spaces and escape of pus is easier.

Value of Chemotherapy.—The report on the use of cod liver oil ointment by Aldrich³⁰⁸ stimulated Wolferman and Adams³⁰⁹ to make up an ointment consisting of white wax, standard cod liver oil and sulfathiazole or sulfanilamide. They believe that the addition of either sulfonamide compound will compensate for the deficiency in bacteriostatic power of the cod liver oil ointment and render it useful both as an adjunct to the Orr method of treating chronic osteomyelitis and as a local application to extensive abrasions and superficial burns. These authors also feel that the use of fine-meshed old sheeting or linen, which has practically no interstices, is a definite factor in promoting healing in wounds. They have found that a mixture of 40 per cent white wax and 60 per cent cod liver oil is satisfactory. The wax is melted over a Bunsen burner, and then standard cod liver oil is added. By rapid stirring and continued heating, lumping can be prevented. The mixture is then cooked for at least an hour and a half and allowed to cool. Enough sulfathiazole or sulfanilamide is then added to make 6 per cent ointment. When the ointment has been autoclaved it is ready for use. These authors' experience with this ointment is limited as yet, but they believe there is sufficient evidence to permit recommending it to others for trial.

[ED. NOTE.—Finely meshed material and the simple preparation the authors describe appeal to the editors as worthy of further trial in the hands of other observers. One of the disadvantages of loose mesh gauze is that the loose strands that become embedded in the wound are difficult to remove at times. Any practical modification of the valuable Orr treatment is worthy of a trial in other clinics.]

Cantor³¹⁰ reports 1 case of chronic osteomyelitis treated by sprinkling sulfanilamide powder into the wound and covering it with antipeol ointment. This, in the author's opinion, stimulated this wound to a remarkable degree. The antiviral, "antipeol," is prepared from sterile filtrates of *Staphylococcus aureus*, *Staph. albus* and *Staph. citreus*, *Streptococcus pyogenes*, *Str. viridans* and *Str. hemolyticus*, and *Bacillus pyocyaneus* and is mixed with a base of hydrous wool fat containing zinc oxide, ichthammol (ammonium sulfoichthyolate) and sodium borate. The author points out that this antiviral does not have an actual bactericidal effect but that it prevents the development of the bacteria, thus bringing growth to a standstill.

308. Aldrich, R. H.: Cod Liver Oil Ointment in Surgery: Eight-Year Study, *Indust. Med.* **11**:153-157 (April) 1942.

309. Wolferman, S. J., and Adams, W. F.: Cod Liver Oil Ointment with Sulfonamides in Wounds and Osteomyelitis, *Indust. Med.* **11**:318-319 (July) 1942.

310. Cantor, I. B.: Osteomyelitis: Report of Case, *J. M. A. Georgia* **31**:249-250 (June) 1942.

The clinical use of penicillin is discussed by Herrell and his associates.³¹¹ The authors state that, while this highly soluble drug may be given by mouth, care must be taken to introduce the material into the duodenum, and they are of the opinion that continuous or nearly continuous intravenous administration is the method of choice at present. These authors suggest that the only method of identifying the material in the tissues and in the urine is by means of a biologic test and that because of the limited amount of penicillin available only 4 of their patients have received it. In all of these the organism was *Staph. aureus*, and the outcome was strikingly satisfactory.

They report a case in which penicillin was used on a white man 33 years of age who was admitted to the hospital because of marked cellulitis of the nose and edema of the right eyelid and of the right side of the face and neck. The sub-maxillary glands on the right were enlarged and tender, and his temperature on admission was 104 F. Diagnosis of extensive cellulitis of the face and orbit was made, and the possibility of a cavernous sinus thrombosis was considered. The patient had a positive blood culture of *Staph. aureus* as well as a positive culture of the same organism from the right nasal passage. Penicillin was administered intravenously after the unsatisfactory course during the first twenty-six hours when sulfadiazine was used. Penicillin was administered at the rate of 25 to 30 drops a minute of a solution in which 115 mg. of penicillin was dissolved in a liter of isotonic solution of sodium chloride. A blood culture made twenty-two hours after the beginning of this treatment was sterile, and two hours later the patient's temperature was 100 F. At no time was there evidence of toxicity which might be attributed to the use of penicillin, and the temperature returned to normal and stayed there after seven days. The patient recovered.

[ED. NOTE.—This is a drug that one will doubtless hear a great deal more about in the future, for it would seem to be amazingly useful in treatment of infection due to *Staph. aureus*. The technical difficulties in preparing the material plus its use by the armed forces have to a great degree retarded widespread clinical use of penicillin in civil practice.]

The introduction of Blaisdell and Harmon's³¹² article on suppurative disease of the joints deals with the historical aspect of its treatment. They stress the important contributions of Hibbs, who contended that pus within a joint was a main factor in the destruction of cartilage and that to lessen this damage surgical drainage of the joint was necessary, and Phemister, who demonstrated the destructive element in pus which destroyed cartilage and established the fact that pressure in the presence of a pyogenic exudate accelerated the erosion of cartilage. The modern trend of treatment has been toward conservatism, and roentgen visualization has enabled the surgeon to be directed intelligently toward diagnosis and treatment of osseous suppuration. Until the recent advent of chemotherapy, few contributions of major importance followed those of Phemister. However, the authors feel that the quality of treatment has steadily improved, and with it the end results.

They state:

The purpose of this paper is to emphasize the need for early and prompt bacteriological diagnosis by joint aspiration and vigorous and meticulous therapy including the prolonged

311. Herrell, W. E.; Heilman, D. H., and Williams, H. L.: The Clinical Use of Penicillin, *Proc. Staff Meet.*, Mayo Clin. **17**:609-616 (Dec. 30) 1942.

312. Blaisdell, J., and Harmon, P. H.: Suppurative Joint Disease and Its Relation to Pyogenic Osteomyelitis: Review of End Results of Sixty-Seven Involved Joints in Fifty-Seven Patients; *Modern Chemotherapeutics, Surg., Gynec. & Obst.* **74**:796-808 (April) 1942.

application of traction to the involved extremity and to describe the application of specific chemotherapy, both during the acute stage and as used to heal the wound. The employment of traction results in a greater percentage of movable joints in the end-results.

The patient with suppurative articular disease presents himself with a painful, swollen, and immobile joint, splinted by spasm of neighboring muscles. Symptoms and findings of acute or subacute infection are present. The chief conditions considered in the differential diagnosis are: acute rheumatic fever; sympathetic sterile effusion in the joint produced by trauma or neighboring infection; intermittent hydroarthrosis, articular tuberculosis (the acuteness of suppurative articular disease usually prevents confusion); hemophilia; traumatic hemarthrosis; acute rheumatoid arthritis; acute bursitis, periarticular cellulitis, and small fractures and sprains. In deep lying joints, the local extension in the joint may be masked by pain and muscular spasm; therefore, the presence of pus within the joint can be determined only by aspiration. This procedure is further indicated at the earliest possible moment for obtaining material for smears and cultures, as well as being the first step in treatment, since suppurative products should not be allowed to accumulate. Roentgen examination of the part should be made immediately. No osseous alterations can be expected prior to seven to fourteen days after onset; however, an early roentgenogram enables the surgeon to rule out preexisting disease of the bone. The earliest finding is that of narrowing of the joint space, and for this reason a roentgenogram of the corresponding joint should be taken.

The treatment of acute suppurative articular disease should be designed to preserve motion if possible and to relieve pain and minimize damage to the joint by aspiration (or arthrotomy if indicated) and traction. Chemotherapy aids in controlling suppuration and in sterilizing the blood stream when involved. The necessity of early diagnosis by joint aspiration and bacterial culture and smear is stressed, since the proper chemotherapeutic agent is selected on the basis of the results from bacterial culture and smear. When this information is lacking during the first few hours, the agents that are active against hemolytic *Staph. aureus* (sulfathiazole and sulfadiazine) are to be used presumptively. For children who have acute articular complications following infection of the upper respiratory tract and of the middle ear, sulfanilamide is to be used.

Two cases are reported, in 1 of which the patient was treated successfully for suppurative disease of the left knee (with foreign body) by aspiration, traction, sulfathiazole and arthrotomy to permit removal of the foreign body and facilitate drainage. Drains which were inserted at the time of arthrotomy were removed on the fifth postoperative day, and on the twenty-third postoperative day the wound was healed and has remained so without recurrence of symptoms. (This was a case uncomplicated by osteomyelitis.) The second case is that of a 26 year old man with a history of osteomyelitis of the distal portion of the right femur of twelve years' duration, with extension of the process to involve the right knee. In spite of chemotherapy and traction, pain on motion of the affected joint persisted, and because of the extensive involvement of the femur pathologic fracture was feared. A long leg cast was therefore applied.

As a result of determination of the concentration of sulfathiazole in the blood and the knee joints of patients who presented sterile effusions in which the concentration of the drug in the aspirated joint fluid was found to be approximately two thirds of that present in the blood, the authors feel that perhaps an increasing number of primary operations can be performed on chronic suppurative joints without danger of sinuses developing when sulfonamide drugs are used both locally and by mouth after operation. They state that the restrictions in operating on bone

which was formerly the seat of infection can be relaxed if local and systemic chemotherapy is utilized. However, the limitations associated with this new auxiliary are not as yet defined and are still under investigation.

[ED. NOTE.—This article is well illustrated and is a review of 67 involved joints in 57 patients. From these data, the most frequently involved joints by suppuration were found to be, in the order named: hip, knee, ankle, shoulder, elbow and wrist.]

Toumey³¹³ discusses the treatment of chronic osteomyelitis with sinus formation. He has found the following plan most effective:

1. Oral chemotherapy is begun one week preceding operation. He uses either sulfathiazole or sulfadiazine, taking the usual precautions. Four grams is given initially, followed by 1 Gm. every four hours.

2. At operation débridement and saucerization are carried out. Four to 10 Gm. of sulfathiazole is dusted into the layers of the wound as it is closed. A plaster cast is then applied.

3. Oral chemotherapy is continued for a week. Two cases are reported, in which the infection remained healed after nine months and five months respectively.

McKeown³¹⁴ makes a preliminary report of 6 unselected consecutive cases of osteomyelitis in children from 9 to 14 years of age. Three patients were boys, and 3 were girls. The surgical treatment was minimal. It consisted of incision of the periosteum and drilling of the bone in the acute stage of the disease and sequestrectomy done later if needed. The dose of sulfathiazole was 1 Gm. per 20 pounds (9.1 Kg.) of body weight. The patients were divided into two groups. The patients in group I were given the drug at the onset of the disease. Administration was continued for eight days, followed by an interval of three weeks, after which the treatment was repeated if necessary. The patients in group II were given the drug twelve to forty-eight days after the onset of the disease, and the dose was repeated as required. In the latter group operation was performed before sulfathiazole was given. In 2 cases of each group *Staph. aureus* was the etiologic agent. Only one blood culture was made and that was negative. The osteomyelitis occurred in the femur in 4 cases, in the tibia in 1 case and in the humerus in 1 case. Plaster of paris was applied in the cases of 3 of the patients, all in group I. Petrolatum gauze packing was used for 2 patients of group I.

The author reached the following conclusions:

1. In no patient was there spreading and gross involvement of bone.
2. In group I the total bony involvement was minimal; in group II the bony change was more marked.
3. Duration of treatment for group I was five months; for group II it was eleven months.
4. Duration of treatment was one half of the average of the previous five years, when sulfathiazole was not in use.

[ED. NOTE.—1. There was no uniformity of studies (blood cultures or determinations of blood sulfathiazole levels or of etiologic agents). 2. In the description of group II there was nothing to indicate whether plaster of paris or petrolatum gauze was or was not used. Hence comparison of the results from early and from late administration of sulfathiazole is not complete, since the other factors were not controlled.]

313. Toumey, J. W.: Chemotherapy in Osteomyelitis, *Lahey Clin. Bull.* **3**:12-16 (July) 1942.

314. McKeown, K. C.: Conservative Treatment of Osteomyelitis, *Proc. Roy. Soc. Med.* **35**:215-217 (Jan.) 1942.

Wilensky³¹⁵ discusses the value of chemotherapy in the treatment of osteomyelitis, giving a résumé of the technical information with comments on the general phenomena involving the body as a whole and the local phenomena involving any particular area, tissue or organ of the body. In the acute hematogenous osteomyelitis he feels that the only stage in which any chemotherapeutic, bacteriostatic or bacteriocidal effect is to be expected from chemotherapy is when bacteremia is present. He points out that should additional numbers of bacteria be continuously shed into the blood stream from an infected blood clot, chemotherapy will have no apparent effect on the positive blood cultures. It will not have a lasting effect unless all local lesions which may produce bacteremia have been thoroughly removed by surgical means.

He feels that the use of sulfonamide compounds may have a definite place as a prophylactic and advises preparing certain classes of patients preoperatively to eliminate certain postoperative reactions and infections. He cites the methods by which sulfanilamide, sulfapyridine, sulfathiazole and sodium sulfapyridine can be administered and feels that all of these drugs act by inhibiting the biologic activities of the bacteria but that the actual destruction of bacteriolysins is accomplished by the ordinary antibacterial agencies of the body. The sulfonamide compounds act only by intimate contact with the offending bacteria and not when the bacteria are locked away out of ready contact with the circulating body fluid. The results are not always predictable under the best of circumstances, and he feels that treatment of osteomyelitis with sulfanilamide and its derivatives has not produced the startling results noted in certain other conditions, especially pneumonia. Sometimes the beneficent results have occurred spontaneously, and for the present, a final evaluation of the value of the sulfonamide compounds in treating osteomyelitis must be guarded.

[ED. NOTE.—This long article clearly points out some of the limitations of the use of sulfonamide compounds, but the author apparently is rather pessimistic about the beneficent results obtained in both acute and chronic osteomyelitis unless there are both an accompanying bacteremia and adequate surgical intervention. It is interesting to recall the enthusiastic acceptance accorded the local and systemic use of sulfonamide compounds in acute war injuries. To date success has been greater in certain medical conditions, though the mounting favorable statistics on the local therapy of war wounds are striking.]

Infection of Muscles.—Cockrell³¹⁶ describes a condition that in the eastern tropics is called myositis purulenta tropica. It is an inflammation of the muscles, which is usually acute and of bacterial origin with signs of acute infection. The lesions may be single or multiple. The cause is most often infection with *Staph. aureus*, streptococci, *Escherichia coli* or a combination of the three. In 25 per cent of the cases there is preexisting pulmonary infection. The muscles show hyaline, granular or fatty degeneration. The disease occurs in persons of all ages and of both sexes, but more frequently in males than in females. The onset is sudden and resembles that of pyemia or septicemia. When localized, the swelling has a board-like consistency until suppuration occurs, as it usually does in one or two weeks. It is hard to diagnose and is often confused with appendicitis, hematoma, perinephric abscess, tuberculosis of the hip or spine, psoas abscess (tuberculosis), trichinosis, filariasis, parasitic infections, bruises, injuries and insect bites. The

315. Wilensky, O.: Value of Chemotherapy in Treatment of Osteomyelitis, *Arch. Surg.* 44:234-259 (Feb.) 1942.

316. Cockrell, B. A.: Primary Suppurative Myositis, *M. Bull. Vet. Admin.* 19:171-177 (Oct.) 1942.

treatment, in general, is supportive. Other forms of therapy include the administration of sulfonamide compounds, local application of hot wet dressings and surgical drainage instituted as soon as indicated. Every effort should be made to avoid contractures and muscular atrophy.

The author reviews 133 cases, most of which were from the South Pacific, although 25 occurred in the United States. In many of the cases the disease was probably misdiagnosed as cellulitis, abscess or psoas abscess of tuberculous origin.

Goldman³¹⁷ states that inflammatory lesions of muscles are rare and are usually classified as (1) primary suppurative myositis, (2) dermatomyositis, (3) neuro-myositis, (4) primary myositis fibrosa and (5) progressive myositis ossificans.

He reports the case of a 63 year old Jew. At onset there was a cracking, vesiculated and keratotic eruption on the hands and between the toes. This improved after treatment with a salicylic acid ointment. The next sign noted was puffiness of the hands and face. Physical examination revealed early lenticular opacities of both eyes but otherwise nothing abnormal. The results of laboratory studies were essentially normal. One year later there were swelling and dermatitis of the hands and feet with an occasional generalized eruption, which was thought to be due to a fungous infection. Stiffness and pain in the right leg developed later and were followed by swelling of the fingers. An electrocardiogram showed low voltage in all leads and an inverted T wave in lead I. Thyroid was given without effect. Pain in the arms continued, and four months after his third examination there was sudden onset of generalized muscular weakness and acute difficulty in swallowing and phonation. The impression was that of atypical bulbar palsy with no fibrillary tremors. There were wasting of muscles, weakness of the pharyngeal muscles and diminished vibratory sense. The clinical impression was that the patient had polyneuritis and myasthenia. Intravenous administration of thiamine hydrochloride and prostigmine bromide resulted in some improvement in vibratory sense, but dysphagia increased and the patient died.

At autopsy the skin was clear. There were atrophy and paleness of the cervical and trunk muscles. There were milk spots on the epicardium, and the spleen was small and fibrotic. The cranial bones were softer than normal. There was slight congestion over the cerebral cortex. The skeletal muscles showed hyaline degeneration with infiltration of lymphocytes, monocytes and polymorphonuclear cells. There was also generalized arteriosclerosis with extreme malnutrition. The neuropathologic diagnosis was "chronic cell change" in the medulla and the cerebral cortex.

The author believes that the early cutaneous lesions are indicative of dermatomyositis and refers to a similar condition reported by Hendry and Anderson in which cutaneous changes antedated involvement of muscles. He calls this a case of polymyositis and says that one or more biopsies of skin and muscle should have been done early in the study.

(To Be Continued)

317. Goldman, D.: Polymyositis: Report of Fatal Case, Arch. Int. Med. 70:822-828 (Nov.) 1942.

Special Notes

SECTION ON SURGERY, GENERAL AND ABDOMINAL, OF AMERICAN MEDICAL ASSOCIATION

Applications for places on the program of the Section on Surgery, General and Abdominal, for the next Annual Session, to be held in Chicago, June 12 to 16, 1944, are now being received. All Fellows of the American Medical Association are eligible. Essayists who are not Fellows may be accepted by invitation. Applications should be addressed to Dr. Alton Ochsner, 1430 Tulane Avenue, New Orleans 13.

Because of the lateness of this announcement, the closing date for applications has been extended to December 31.

CORRECTION

In the article by Dr. D. J. Leithauser entitled "Confinement to Bed for Only Twenty-Four Hours After Operation: A Means of Preventing Pulmonary and Circulatory Complications and of Shortening the Period of Convalescence," in the August issue (ARCH. SURG. 47:203, 1943), the second word of the ninth line in the report of case 10, on page 213, should be "thirtieth" instead of "thirteenth."

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CANCER ASSOCIATED WITH ACANTHOSIS NIGRICANS

REVIEW OF LITERATURE AND REPORT OF A CASE OF ACANTHOSIS
NIGRICANS WITH CANCER OF THE BREAST

HELEN OLLENDORFF CURTH, M.D.

NEW YORK

Acanthosis nigricans, rather widely discussed in dermatologic handbooks and journals,¹ has been strangely neglected in medical and surgical literature and in publications dealing with cancer. This is the more difficult to understand since in a great number of cases the occurrence of this characteristic cutaneous disease in itself suggests the presence of a coexisting internal cancer in the patient.

The association with cancer occurs in 49.74 per cent of all cases of acanthosis nigricans. So far 384 cases of the disease have been reported.

The study of a noncancerous disease associated with cancer under definite conditions offers great advantage to cancer research, which becomes wider by the additional investigation of the associated phenomenon and of its relationship to cancer. It is particularly fortunate that this associated phenomenon is represented by a well defined disease of the skin visible at early stages of development.

DEFINITION

Acanthosis nigricans is a benign disease of the skin which is clinically characterized by exaggeration of the cutaneous folds and brownish to blackish discoloration. It has a number of sites of predilection, of which the axillas are the most common (fig. 1). The mucous membranes may also be involved. The palms and plantar surfaces may show hyperkeratoses. Papillomas, pigmented spots and verruca-like changes may accompany the characteristic cutaneous changes. Histologic examination of the affected skin reveals hyperkeratosis, papillary hypertrophy, acanthosis and an increase in pigment, mostly in the basal layer.

Acanthosis nigricans occurs in two types: One type of acanthosis nigricans is associated with cancer of an internal organ, and is therefore falsely called malignant. The type of the disease not so associated is called benign. Of the 384 cases, 193 were of the benign and 191 of the malignant type. Cancer of the skin never develops from the cutaneous lesion of acanthosis nigricans, nor is it a cutaneous metastasis of an internal cancer, as has been described in connection with gastric cancer by Fasal and by Bourdillon. Since this paper was submitted for publication 11 additional cases of acanthosis nigricans have been reported, bringing the total number of cases to 395. Of these 11 cases, 5 were instances of the malignant type (Jeanneret; Silver; Sayer; Gunche, Iapalucci and Troncoso),

From the Department of Dermatology, College of Physicians and Surgeons, Columbia University.

1. Extensive reviews of cases are found in the monographs of Moncorps and Michy. Curth's paper (1936) contains a discussion of the causes of acanthosis nigricans.

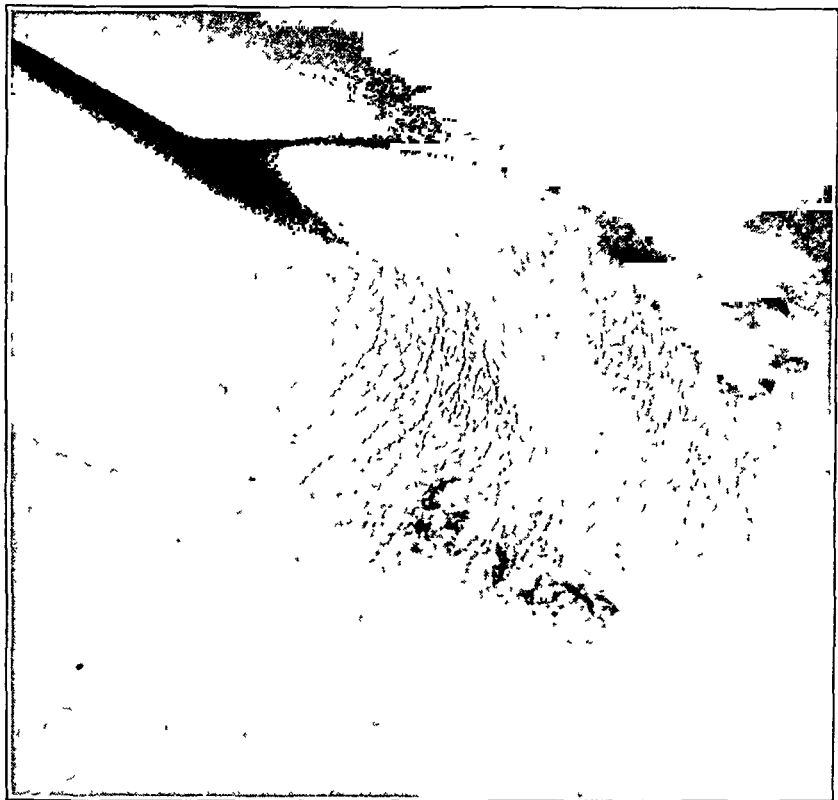


Fig. 1.—Benign acanthosis nigricans of the axilla.

TABLE 1.—Two Types of Acanthosis Nigricans

	Malignant (Never Malignant in Itself and Not a Metastasis)	Benign (Sometimes Called Juvenile)
Incidence... ..	About 50% of all cases	About 50% of all cases
Combination with cancer....	Cancer in patient	No cancer in patient
Histology.....	Identical (see text)	Identical (see text)
Sex.....	Both sexes	Both sexes
Age at onset (no sharp division of types should be based on age)	Mostly middle aged, also young and old persons	Usually at birth or in early years of life, but may appear or spread at puberty; caution with patients past second decade
Distribution.	Symmetric	Symmetric or unilateral (neviform); Curth (1936) described a boy born with unilateral neviform acanthosis nigricans who showed symmetric acanthosis nigricans at and after puberty
Course.....	Mostly spreading; fatal outcome due to accompanying malignant tumor	Spreading at onset, later mostly stationary or regressing; duration indefinite
Familial cases.	Not reported	Occasionally in one generation or two or three generations
Cases of "mixed" type	<div>1 Baby born with unilateral acanthosis nigricans; later symmetric involvement of skin; death at age of 2 years from malignant tumor of abdomen (Halty, Correa Delgado and Volpé)</div> <div>2 Thirty-six year old man with acanthosis nigricans of left elbow of fifteen years' duration; recent extension over body and mucous membranes; severe cachexia; cancer of stomach probable (Becker)</div>	

3 were reported as cases of the benign type (Walzer; Franks; Garson and Sagnes) and 3 were mentioned by Lahiri without reference as to the type of the disease.

Table 1 briefly shows the characteristic qualities of each type. While acanthosis nigricans is generally distributed symmetrically, the benign form may occur on one

side of the body only. Many cases which have been listed as instances of ichthyosiform or acanthotic unilateral nevoid eruptions seem in fact to have been cases of benign acanthosis nigricans (Hitaka and others).

IDENTITY OF THE BENIGN AND THE MALIGNANT TYPE

The belief that benign and malignant acanthosis nigricans are the same is based chiefly on the identity of the histologic and macroscopic features of the two types.

Table 1 illustrates the possibility of transitional development: first, from unilateral benign acanthosis nigricans alone to a combination with symmetric benign acanthosis nigricans (Curth, case 1; Franks²); second, from unilateral acanthosis nigricans to symmetric malignant acanthosis nigricans (Becker); and it also shows the association with cancer of unilateral acanthosis nigricans in a baby dying from a malignant tumor (Halty, Correa Delgado and Volpé). Cases such as Becker's and Halty, Correa Delgado and Volpé's, showing characteristics of each type successively or simultaneously, will go far to strengthen the unitary conception of acanthosis nigricans.

How complicated classification of a case can be is illustrated by Freund's report of a 28 year old woman who had suffered from widespread symmetric acanthosis nigricans since the age of 9 years. When she was 27 multiple cancers of the breast rapidly developed. This case, of course, was of the malignant type, but eighteen years elapsed before the accompanying cancer manifested itself.

THE PRESENCE OF ACANTHOSIS NIGRICANS AND CANCER IN THE SAME PATIENT IS NOT COINCIDENTAL

Cancer is no mere coincidence in cases of acanthosis nigricans. Even if the so-called benign form is disregarded for the present, it is still true that 50 per cent of patients with a noncancerous disease suffer also from cancer. This is a much higher percentage of simultaneous occurrence with cancer than any other noncancerous disease would show.

In most cases of malignant acanthosis nigricans the two diseases become manifest at about the same time and run a parallel course. The cutaneous disease will show intensification and spreading to remote places at a time when the tumor is also progressive. There are several cases of malignant acanthosis nigricans on record in which simultaneous development of the two diseases assumed enormous proportions. I cite the following instances:

CASE 1 (Hengstenberg).—A man aged 49 had suffered for five years from gastric disturbances (pain, belching and low gastric acidity). Acanthosis nigricans had been present on typical areas for five or six weeks. Examination revealed a large inoperable tumor of the stomach and an enlarged supraclavicular lymph node on the left side. Acanthosis nigricans gradually involved the skin of the entire body and part of the mucous membranes. Death occurred after one year. Autopsy revealed cancer of the stomach with involvement of the liver and also retroperitoneal cancer behind the stomach near the pancreas. Metastases of the third lumbar vertebra and of the bronchial, mediastinal and left supraclavicular lymph glands were found. Large tumor masses were seen at the upper part of the left kidney with destruction of the left adrenal. Acanthosis nigricans involved the skin and the mucous membranes.

CASE 2 (Dubreuilh).—A man of 22 had suffered for many years from nausea and vomiting and acanthosis nigricans. For four months nausea and hyperpigmentation had been increasing. Examination revealed a large hard tender tumor in the left hypochondrium and five to six enlarged lymph nodes in the left supraclavicular fossa. Acanthosis nigricans became general-

2. Major Franks reports a case of a soldier who had had an epidermal nevus on the left side of the abdomen since birth and who had acquired symmetric acanthosis nigricans in the five months before he was examined. Exploratory laparotomy gave negative results. It seems that too short a time has elapsed to permit with any certainty classification of the type to which this patient's eruption belongs.

ized (the feet and the nails of the thumbs remained the only areas not involved). The tumor became larger, and generalized adenopathy was found. Death occurred after four months. Autopsy revealed peritonitis, ulcerated carcinoma of the pyloric region and tumorous lymph glands behind the stomach and in the mesentery. The lymphatic vessels of the intestines and the adrenals, the only internal organs examined histologically, were filled with neoplastic cells. The adrenals themselves were not destroyed. Acanthosis nigricans of the skin was verified histologically. Cancerous injection of the lymph vessels without inflammatory reaction of the neighboring tissue occurred in the deep skin or on the border of the hypoderm. These masses sometimes looked like a glandular cancer. Microscopic examination of all the internal organs was not undertaken, since death occurred during the first World War in a field hospital.

Hue speaks of *rapidité effrayante* with which in his case cancer of the uterus spread in a few weeks. During this period more and larger areas of skin showed acanthosis nigricans. In the cases of Lapa, Archangelskij, Schalek, de Azua and Ducuing, who spoke of "acute" acanthosis nigricans, the cutaneous changes spread equally rapidly. In Scolari's and Dubreuilh's cases, the papillomatosis of the skin was especially conspicuous. In all of these cases rapid generalization of the cancer, which led to early death, accompanied the cutaneous changes.

The parallelism between the two diseases even goes so far that there is occasional regression, however transitory, of the cutaneous lesions after attempted removal of the accompanying tumor. It was seen in the cases of Kadono and Morino, Fuse, Spietschka (case 3), Hodara, Friedel, Kaposi and Joseph. Cancers in these cases involved various organs. Zollikofer reported that his patient noticed a decrease of the pruritus after resection of gastric carcinoma. In Spietschka's case, the only one of this series which was followed up, the lesions reappeared one and one-half years after operation for chorionic carcinoma at a time when a glandular metastasis was noticed. Reports of other cases do not mention even temporary improvement of acanthosis nigricans after operation.

One still may argue that a comparatively large number of middle-aged people will have cancer whether they are suffering from acanthosis nigricans or not. However, there are records of many young people with acanthosis nigricans and cancer (table 2). The significance of this high percentage of young people with cancer of the stomach especially becomes obvious when one realizes that cancer of the stomach is usually regarded as a problem for the age group over 40.

The following report is of a case which had been observed by Dr. Beatrice Kesten^{2a} and by the surgical department of the Presbyterian Hospital of New York. Dr. Virginia Kneeland Frantz gave me all the information she could gather on the pathologic changes. The patient died at home. Permission for opening the thoracic cavity was not given.

In spite of the incomplete autopsy, the case merits publication because of the infrequently observed combination of acanthosis nigricans with cancer of the breast.

REPORT OF CASE

The patient, a married American woman 47 years old, was first examined in November 1938.

History.—Menses had started at the age of 11. The patient had one child, 18 years old, who was well. An operation for the removal of uterine fibroids, a salpingo-oophorectomy on the right side and an appendectomy were performed when the patient was 23 (1914). In 1932, cutaneous lesions on the body started to develop, one year after the diagnosis of recurrent fibroids had been made. For years she had noticed a swelling of the left lobe of the thyroid gland which seemed related to the menstrual period. For eight weeks a nodule in the right breast had been noticeable. Her chief complaints were abdominal pain and frequency of urination and, during the past month, unbearable itching and increasing roughness and darkness of the skin.

2a. The case is included in this series by special permission of Dr. Kesten.

TABLE 2.—*Cancer in Young People with Acanthosis Nigricans*

Authors	Age	Sex	Tumor	Verification of Malignancy	Classification of Tumor	Comment	Course
1 Halcy, Correa Delgado and Volpé.....	2½	F	Abdominal tumor (inoperable)	Autopsy	Malignant tumor	Died
2 Naruo, cited by Sekiba.....	9*	F	Cancer of stomach	Clinical picture	Acanthosis nigricans for 5 years	No report
3 Lipskerof.....	17	F	Cancer of stomach (?)	Clinical picture	Oachexia
4 Herold, Kaufman and Smith.....	17	F	Gastric cancer with metastases	Laparotomy	Alveolar gastric carcinoma	Died
5 Spletetchka.....	20	F	Ochorionic carcinoma	Operation	Chorionic carcinoma	Metastasis
6 Dubreuilh.....	22	M	Gastric cancer with metastases	Autopsy	Cancer of stomach	Died
7 Yamada.....	23	F	Cancer of pylorus	Clinical picture	No report
8 Flakamp.....	23	F	Gastric cancer with metastases	Autopsy	Cancer of stomach with many metastases	Died
9 Kobayashi.....	23	M	Cancer of liver (?)	Clinical picture	Acanthosis nigricans since age of 12	No report
10 Masson and Montgomery (case 8).....	25	M	Lymphosarcoma of stomach with metastases	Laparotomy	Lymphosarcoma of stomach	Died
11 Lapa.....	26	M	Gastric cancer with metastases	Autopsy	Mucoid adenocarcinoma of stomach	Died
12 Jakubson.....	27	F	Gastric cancer with metastases	Autopsy	Cancer of stomach	Died
13 Archangelskiij.....	27	M	Gastric cancer with metastases	Autopsy	Cancer of stomach with many metastases	Died
14 Freund; Brunetti, Freund and Sturl.....	27	F	Cancer of breast with metastases	Operation	Alveolar cancer of breast	Acanthosis nigricans since age of 9 years	No report
15 Barber.....	27	F	Cancer of stomach (?)	Operation	Tumor inoperable	Alive
16 Masson and Montgomery (case 6).....	29	M	Neoplastic process probable	Clinical picture	Laparotomy 5 months before, negative	Died
17 Hodara.....	30	F	Cancer of breast	Operation	Cancer of breast	Skin worse
18 Darfer.....	30	M	Gastric cancer (inoperable)	Clinical picture	Metastasis
19 Masson and Montgomery (case 2).....	30	M	Cancer of liver (?)	Laparotomy	Adenocarcinoma of liver (?)	Died
20 Millan, Sauphar and Marcron.....	31	F	Abdominal cancer	Autopsy	Squamous cell cancer of lymph glands	Abdominal tumor not investigated	Died
21 Jordan, Schamschlin and Dobrow.....	31	M	Gastric cancer with metastases	Operation	Died
22 Küttner (case 2).....	32	M	Cancer of stomach	Roentgenogram and clinical picture	Gastroenterostomy 2 years before	Patient worse

* Gougetot and Carleaud cited Mukai's observation of 14 patients who had malignant acanthosis nigricans before the age of 10. Mukai, however, listed these cases as benign.

Examination.—Examination revealed a brownish black discoloration of the skin with a few papillary growths in the axillary, antecubital and genitofemoral folds and on the vulva. "Corrugations" were also present on the hard palate. The palms showed hyperkeratoses. There was a pecan-sized swelling in the left upper lobe of the thyroid. In the right breast at 3 o'clock there was a lozenge-shaped mass 3 by 3 by 4 cm. which was freely movable and not tender and not definitely connected with the skin, nipple or thoracic wall. No dimpling of the skin was demonstrable. Enlarged axillary nodes could not be felt. The abdomen showed a well healed lower midline incision. The edge of the liver was palpable on deep inspiration. An irregular nodular mass in the pelvis extended upward almost to the umbilicus, somewhat to the left. The cervix appeared to be healthy. Routine laboratory examination did not furnish any contributory evidence. A diagnosis of acanthosis nigricans, tumor of the

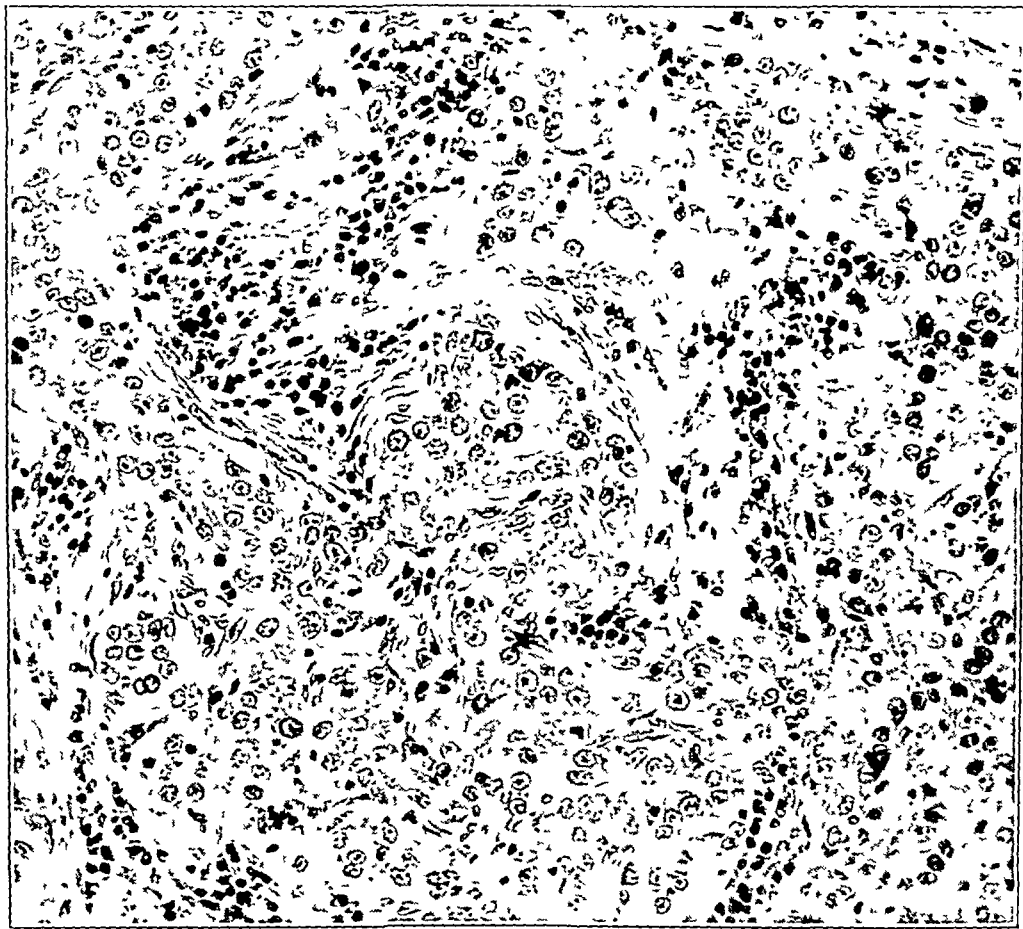


Fig 2—Cancer of the right breast

breast (carcinoma?), tumor of the thyroid gland (nontoxic adenoma?) and fibromyomas of the uterus was made.

Course.—It was decided to explore the tumor of the breast before operating on the fibroids, and the operation was performed Nov. 17, 1938. On section the mass in the right breast was firm and white. There was no capsule, and there seemed to be definite infiltration of this tissue into the breast on the upper inner side. The gross diagnosis of carcinoma was verified by examination of frozen sections.

Complete right mastectomy with removal of pectoral muscles and axillary lymph glands was performed.

Microscopic Report.—Numerous large and small mammary ducts were lined or completely filled by tumor cells, numerous irregular clumps and cords of cancer cells and a few cancerous acini (fig. 2). Within the distorted and enlarged ducts likewise there was a definite tendency

to form rather well defined acini. Throughout the section extensive invasion of the connective tissue and fat was noted, and there was a slight to rather extensive infiltration with lymphocytes and large mononuclear cells. The individual tumor cells showed some variation in size and shape, the majority, however, being round, oval or polyhedral. Basement membranes were well preserved only in the ducts and acini. Elsewhere this structure was lacking and the tumor appeared to be growing irregularly. The nuclei showed about the same degree of variation as the cells. They were moderately chromatic and frequently had prominent nucleoli. Polarity was generally lost. Mitoses averaged about 1 in every two or three high power fields, and some were rather bizarre. At different points in the periphery relatively normal breast tissue was present. The section stained with mucicarmin failed to show any intracellular mucin.

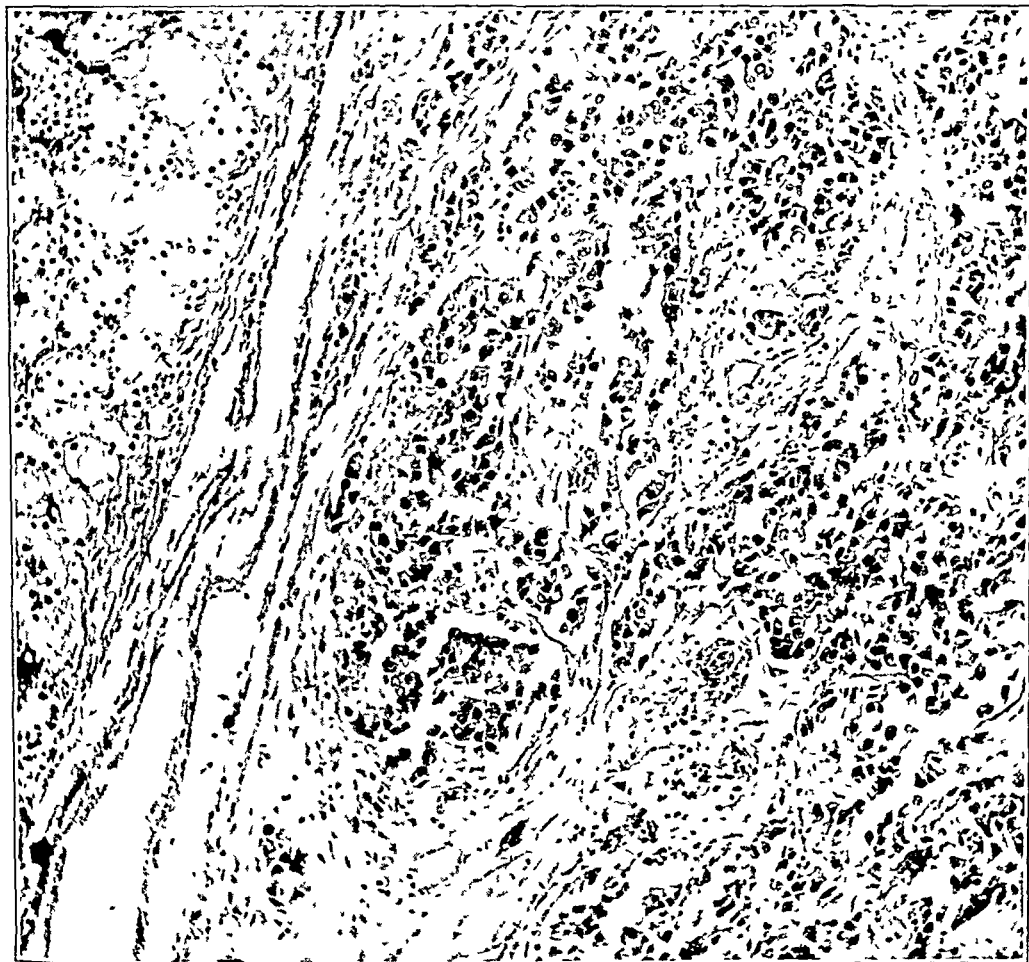


Fig 3 (case 3).—Metastatic carcinoma of the left kidney.

Besides the tumor, there was evidence of mild mamillitis and chronic cystic mastitis of the right breast with rather marked epithelial hyperplasia.

Thirty-seven lymph nodes were found. Several appeared rather hard, and none contained tumor tissue.

The tumor was diagnosed as carcinoma (grade 2) of the breast, mostly intraductal. No invasion of lymph nodes, blood vessels or nerves was seen.

Further Course.—On December 1 supravaginal hysterectomy and left salpingo-oophorectomy were performed. The uterus had the size of a pregnancy of four and one-half months. The histologic diagnosis was fibromyomas of the uterus. Besides a practically normal left tube and follicular serous cysts of the left ovary, an old corpus luteum was found. At this operation pericholecystic postinfectious adhesions and a distended gallbladder were seen, but no signs of metastases.

In May and in November 1939, when the patient returned to the clinic for a check-up, no metastases of the tumor of the breast were found.

Four days after the removal of the right breast improvement of the itching was noted. The cutaneous lesions started to regress and became barely noticeable. When the patient was again seen, in March 1939, the cutaneous lesions had begun to reappear and to spread over wide areas. The papillary hypertrophy of skin and mucous membranes had reached bizarre dimensions. The patient was given six treatments with filtered roentgen rays during September and October on the most involved parts of the skin, with no effect.

In February 1940 a streptococcic sore throat developed, and the patient was rapidly going downhill. Before her death on June 6, she complained of considerable pain in the region of the liver. Permission was given only for removal of a section of the skin and for the

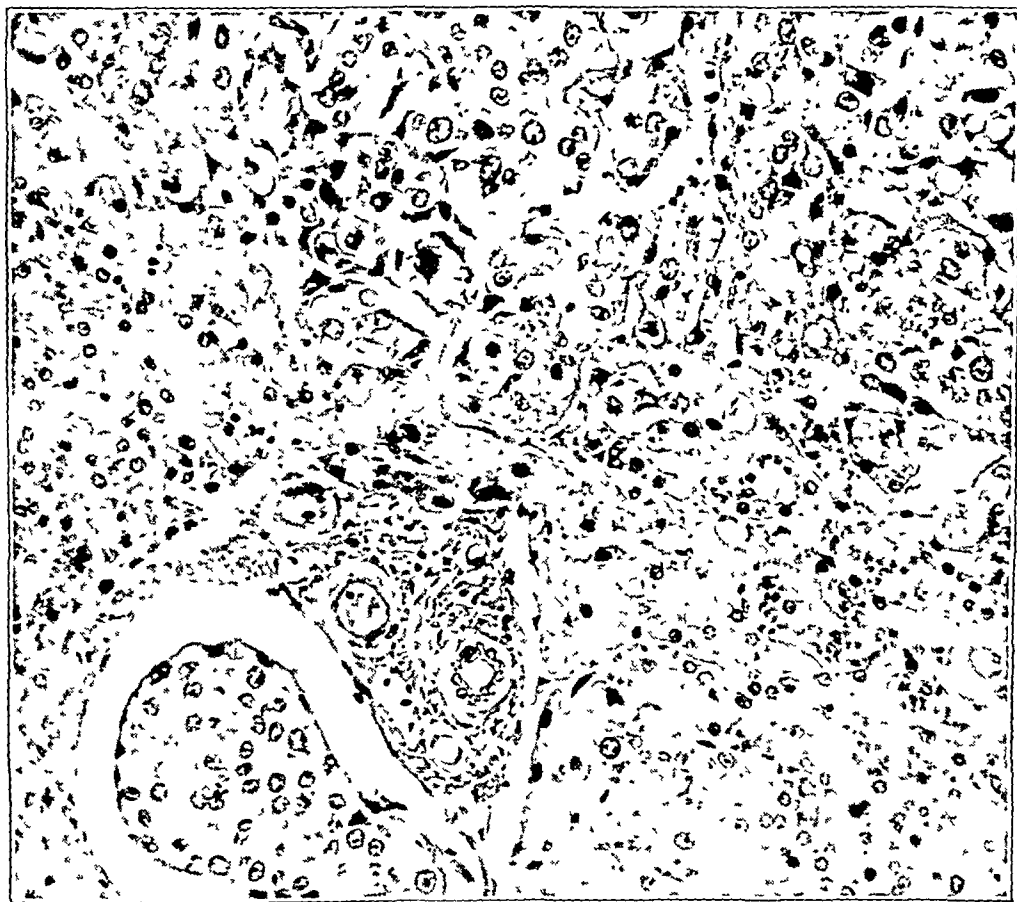


Fig. 4—Metastatic carcinoma of the liver.

opening of the abdomen. The autopsy was performed by Dr. Morris Maslon, of Warren County, N. Y., who has permitted publication of his reports.

Autopsy.—When the abdomen was opened, the liver was found studded with carcinomatous masses. Carcinoma also was present in the left adrenal and in the upper pole of the left kidney (fig. 3).

Section of the liver (fig. 4) showed extensive invasion by a tumor similar to that in the breast, growing in the same cords and sheets, again with little tendency to glandular formation and with no mucin. Mitotic figures were again frequent.

Section of the adrenal (fig. 5) showed a small amount of adrenal cortex present. All the rest of the tissue was tumor. In portions of the tumor the cells showed no cohesion and appeared shrunken and fairly widely separated. In other portions, however, definite glandular arrangement was seen. The cells were large, for the most part polyhedral but sometimes columnar, and the nuclei were much more chromatic than those of the primary tumor. The lumens of the glands contained mucicarminophilic material, and droplets of this were found

in the cytoplasm of many of the cells. Such droplets were also found in the cells which showed less cohesion.

Sections of the skin (fig. 6) showed pronounced hyperkeratosis. The depressions between the sharp projections of the epidermis were filled with lamellated keratin-filled clefts. The papillary layer was wide. Pigmentation of the basal layer was striking. There were also scattered pigment-laden chromatophores in the papillary bodies. There was a slight perivascular infiltration in the corium.

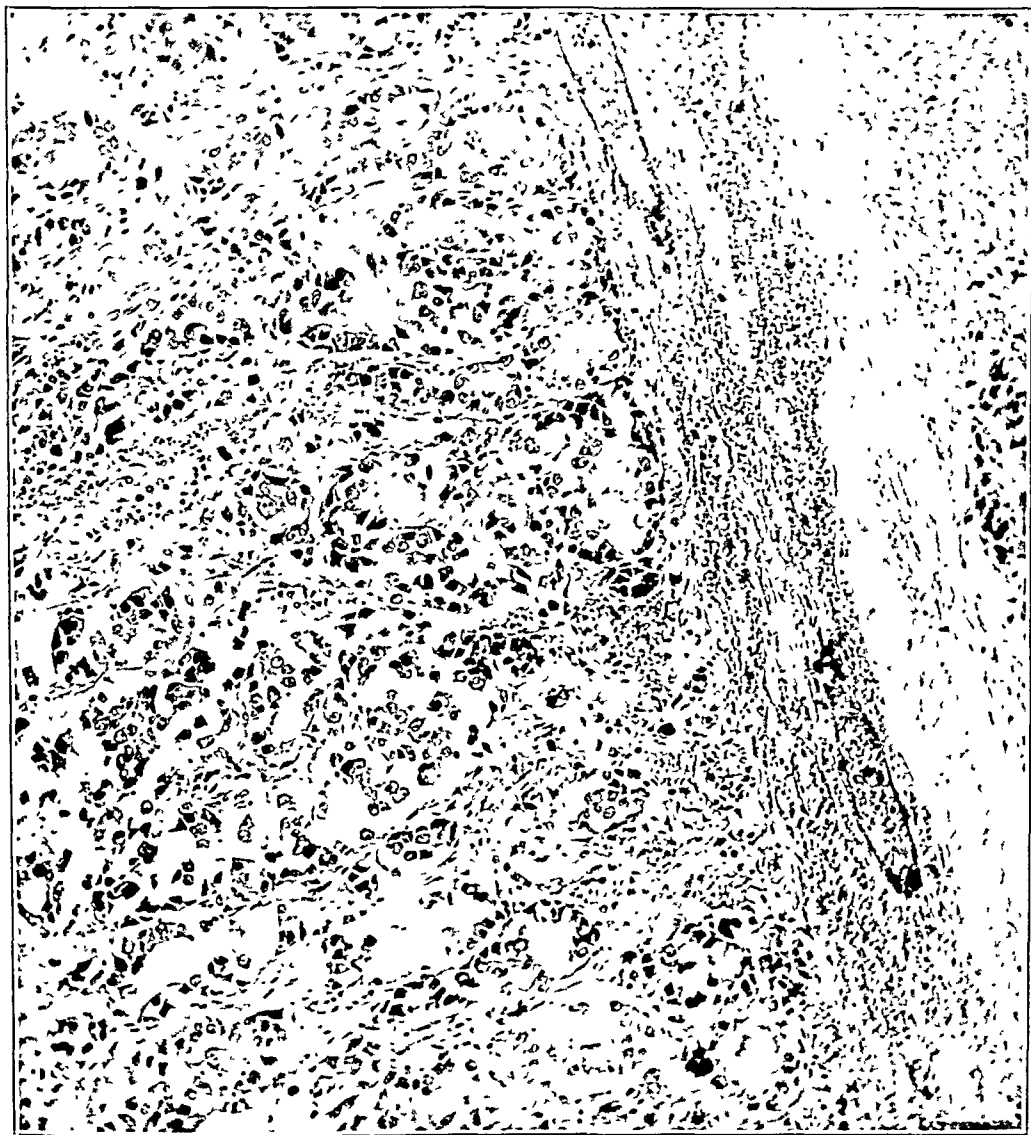


Fig. 5.—Metastatic carcinoma of the left adrenal gland.

A diagnosis of acanthosis nigricans of the skin, associated with carcinoma of the liver, the left kidney and the left adrenal subsequent to carcinoma of the mammary gland was made.

Comment.—The cancer in this case was a primary cancer of the breast. This is the ninth case of mammary carcinoma associated with acanthosis nigricans reported in the literature. Fibromas of the uterus were also seen in Heath's case of mammary cancer. Their occurrence may be coincidental in view of the frequency

of uterine fibroids. The complete and early removal of the mammary cancer, apparently before regional metastasis had occurred, had inspired hope for a better result than was actually obtained. While nothing can be said about metastases in the thoracic cavity in the case reported here, widespread metastases were seen in the liver and in the left kidney and adrenal after a relatively short period. There was alveolar arrangement of the mammary cancer. Clumps, masses and strands of



Fig. 6.—Sections of skin, showing changes due to acanthosis nigricans

tumor cells invaded the connective tissue. The tendency to glandular formation was perhaps more pronounced in the adrenal metastases than in the primary cancer. At the same time that the metastases of the mammary tumor were involving large parts of the abdominal cavity, the changes of the skin and mucous membranes assumed great proportions. Acanthosis nigricans had tended to subside for a while after removal of the tumor. Acanthosis nigricans seems to have definitely appeared six years (1932) before there were symptoms of cancer (1938).

CANCER ASSOCIATED WITH ACANTHOSIS NIGRICANS

Incidence.—The incidence of acanthosis nigricans, and therefore also of cancers associated with it, is low. It is conceivable that in some cases of cancer subsequent appearance of acanthosis nigricans may have been prevented by the death of the patient. More records of abortive forms of the disease may reveal a greater incidence.

Abortive forms of acanthosis nigricans have been described by Miescher, Pollitzer, Barber (?) and Weber. I recently (1942) saw a patient with such a condition in consultation with Dr. Nathan Sobel and Dr. Charles Pines at the Central Clinic of the Bureau of Social Hygiene, of the Department of Health of the City of New York. A woman of 20 requested a test of her blood. During the examination, mild acanthosis nigricans of the sides of the neck and of both axillas involving the hairy parts and extending slightly beyond was found. The presence and duration of the cutaneous changes were unknown to the patient. She had menstruated at the age of 11 years 6 months. Her father had died in 1938 from cancer of the stomach. Her paternal grandmother had died recently in her sixties from cancer of the breast.

Cases of abortive acanthosis nigricans will have to be followed up carefully, and in the case in question the diagnosis will have to be verified.

Distribution.—Acanthosis nigricans has been described in all parts of the world. The first reports came from Germany (Pollitzer) and Austria (Janovsky). All other countries followed. Many cases of acanthosis nigricans occur in Japan. One Japanese author (Toyama) described 6 patients with acanthosis nigricans, 4 of whom suffered from cancer of the stomach; another (Sekiba) described 11 patients with acanthosis nigricans, 6 of whom had gastric cancer. One had a tumor of the liver, and the rest did not show any cancer. Javanese patients were described by Soetomo and by Polak. Most of the American reports concern white persons. American Negroes with acanthosis nigricans were described by Masson and Montgomery (case 5), Schamberg, Conrad and Rapp. The case of an African Negro was reported by Tessitore. Lately, several cases were observed in Mexico (Millán Gutiérrez) and South America (de Anduiza; Halty, Correa Delgado and Volpé; Balina, Braceras and Kaminsky; Castex and Facio; Muschietti and Vázquez; Roffo and Iapalucci; Orol Arias and Landabure; Sánchez Covisa and Brito Foresti and Vignale).

Sex and Age.—Stihl noted a ratio of 49.3 per cent female to 50.7 per cent male patients. The tables in this article give a percentage of 50.3 per cent female and 49.7 per cent male patients.

Table 2 shows that many young people suffer from malignant acanthosis nigricans. The greatest number of patients so affected, however, are middle-aged. Very old people with malignant acanthosis nigricans have been described. The patients of Nakamura, Perman, Tiefel, Lurie, Nicholas and Strandell were 70 years old, and those of Isaac and De Azua were 72. Scolari's was 74 and Wollenberg's 79. The average age is $40\frac{3}{4}$ years (Stihl).

Location of Cancer.—Darier's assertion that 80 per cent of all malignant tumors associated with acanthosis nigricans are abdominal is now only approximately correct. I found the percentage higher (92.67), since the only cases of non-abdominal cancer reported are 9 of mammary cancer (table 3), 3 of cancer of the lung (see table 4), and 2 in which the presence of a mediastinal tumor was suspected.

TABLE 3.—Cancer of Breast in Patients with *Acanthosis Nigricans*

Authors	Age	Site of Tumor	Duration	Verification of Tumor	Classification of Tumor	Extent of Tumor and Metastases	Course	Comment
Heath ?.....	63	2 years	*	Fibromas of uterus; removal of right breast 12 years previously, left breast 5 years previously
Freund; Brunetti, Freund and Sturli..	27	3 cancerous nodules in left breast	6 months	Operation	Adenocarcinoma	Metastases in axillary and supraclavicular glands	Alive	Acanthosis nigricans preceded cancer by 18 years
Hodara.....	30	2 years	Operation	Alive; acanthosis nigricans worse	Acanthosis nigricans appeared after operation
Vereinigung Rheinisch-Westphälischer Dermatologen	57	18 months after amputation	Operation	Carcinoma simplex solidum	Metastases	Alive	Onset of acanthosis nigricans after operation and irradiation of cancer
Matras.....	52	Right breast	8 months after extirpation	Operation; autopsy	Carcinoma solidum scirrhosum of breast; alveolar arrangement of metastases in liver	Metastases to liver	Died
Boeck ?.....	52	Cancerous tumor in abdomen	2 years	No autopsy	Medullary cancer	Metastases in abdomen	Died	Operation for cancer of left breast 4½ years previously
Kutznitzky.....	41	13 months	Autopsy	Regional, abdominal, inguinal lymph glands, pleura, uterus, liver, skull, sternum
Sams.....	40	Carcinoma	Died	Carotenosis
Curth 2.....	47	Right breast	21 months	Operation	Alveolar arrangement	Liver, kidney, left adrenal	Died	Partial autopsy

* No operation was performed when acanthosis nigricans appeared; therefore the question remains open whether another cancer had developed or whether metastases had appeared as was indicated by some clinical observations.

Mukai gave the percentage of gastric cancer among the abdominal cancers as 58 to 61 per cent. I found it to be 69.86 per cent. In table 5 only those of the 102 cases will be listed in which there was cancer of the stomach with metastases. The remainder³ were reported as gastric cancers without detailed information regarding possible metastases. The average duration of tumors of the latter group was 11.65 months, of the tabulated group, twelve months.

Cases of cancer located elsewhere than in the stomach were relatively few. There were 8 cases of cancer of the uterus (table 6) and 12 of cancer of the liver⁴ (table 7). In 4 cases of cancer of the pelvis (table 8) and 8 of abdominal cancer (table 9) the primary tumor could not be precisely located. There were 2 cases each of cancer of the rectum (table 10) and cancer of the intestines (table 11). There was 1 case of cancer of the ovary (table 12) and 1 of probable primary renal cancer.⁵ One questionable case of cancer of the pancreas was reported by Gilchrist (case 2) and 1 by Nägeli. One case suggestive of carcinoma of the esophagus was reported by Velikanoff. There was 1 case of chorionic carcinoma (table 13) and 5 in which metastases were present, but the primary site of the cancer was unknown (table 14).

TABLE 4.—*Cancer of Lung and Cancer of Chest in Patients with Acanthosis Nigricans*

Authors	Age	Sex	Verification of Tumor	Duration	Metastases	Site	Course
Petrini de Galatz.....	47	M	Autopsy	13 months	Pleura, hilus and tracheobronchial glands	Left lung	Died
Dore.....	Roentgenogram	Lung
Wanderer.....	51	M	Roentgenogram; clinical picture	1½ years	Mediastinum	Alive
Levin and Behrman..	59	M	Autopsy	2 years	Pleura, diaphragm, liver, kidney, peritoneum, intestines and right adrenal gland	Extensive carcinoma of left lung	Died

Type of Cancer.—In most of the reports on gastric cancer, adenocarcinoma was seen (Artom [case 1], Toyama [cases 1 and 2] and Roffo and Iapalucci [case 1]). This same type of arrangement was also found in tumor and metastases of the patient of Scolari (cancer of cardia), Mazzanti (muroid adenocarcinoma of the gastric wall with metastases of the liver and glands) and Lapa (muroid adeno-

3. Muschietti and Vázquez; Béron (case 1); Pautrier; Rille (case 1); Birch-Hirschfeld and Kraft (same case as Rille); Nicolas, Gaté and Lebeuf; Friedel; Ducuing, Masson and Montgomery (cases 4 and 5); Damblé; Frick (?); Guérault (?); Tokutomi; Kreibich; Küttner (case 2); Matras; Zollkofer; Fuse; Hermans and Schokking (?); Capelli (case 2); Asahi; Barber; Stanislawsky; Hissard (cases 1 and 2); Strandell (case 1); Becker; Berggreen; Naruo; Hirano; Darier (case 2); Mourek; van Leeuwen; Yamada; Makino; Ishiwatari; Takuwa; Ostwald; Montana; Feit; Bechet (2 cases); Jewsejeff and Posen (?); Kadono and Morino; Gilchrist; Yano; MacCormac (?); Tomaszewski; Kubo and Kohsaka; MacIntosh (?); Vidal.

4. The number of primary hepatic tumors given in this résumé seems very high in view of the rarity of primary carcinoma of the liver. As can be seen from the table, the diagnosis in many of the cases is chiefly based on clinical observations and has not been verified by operation, autopsy or histologic examination. The actual incidence of primary hepatic tumors in connection with acanthosis nigricans seems to be considerably lower.

5. The case reported by Dziobek as an instance of cancer of the kidney in a patient with acanthosis nigricans showed at operation papillomatous carcinoma of the left kidney. No report of further exploration or examination is given.

TABLE 5.—*Cancer of the Stomach with Metastases in Patients with Acanthosis Nigrans*

Authors	Age	Sex	Verification of Tumor	Duration of Tumor	Site of Tumor	Classification of Tumor	Extent of Tumor and Metastases	Comment	Course
Hengstenberg.	49	M	Autopsy	One year	Stomach		Retropertitoneal cancer behind stomach; metastases in liver, left kidney, left adrenal, left suprarenal, bronchomediastinal lymph nodes, 3d lumbar vertebra		Died
Dubreuilh	22	M	Autopsy (partial)	8 months	Pylorus	Metastases in alveolar arrangement	Suprarenal and generalized adenopathy, lymphatic vessels of many inner organs and skin filled with tumorous masses		Died
Artom (case 1)	63	M	Autopsy	About 1 year	Cardia	Ulcerated alveolar carcinoma	Adrenals, pancreas (?), glands in cardiac region and posterior wall of stomach		Died
Perman (case 1)	70	F	No autopsy	10 months	Antrum	Liver, 1 subclavicular gland	Marked polyposis of intestinal tract	Died
Perman (case 2)	55	M	Autopsy	5 months	Lesser curvature		Retropertitoneal tumor, liver, kidney, right adrenal capsule, left adrenal (?), psoas muscle, mesenteric lymph nodes, spine		Died
Toyama	69	M	Autopsy	3 years	Stomach	Adenocarcinoma (colloid)	Retropertitoneal lymph nodes (miliary tuberculosis of omentum)		Died
Tesseraux	50	F	Autopsy	4 6 months	Pylorus	Partly scirrhus, partly cylindric cell carcinoma; glandular and lymph nodes	Right lung, liver, lymph nodes		Died
Burgess.	58	F			Lesser curvature	..	Liver involved		Died
Doutrelepoint; Grouven and Fischer	34	M	Clinical picture	3 years	Stomach		Liver involved		Alive; worse
Pélin ...	46	F	Roentgenogram	1 year	Stomach ?		Liver involved		Died
Sulzberger	63	M	Roentgenogram	3 months	Lesser curvature		Liver involved		Alive
Scolari	74	F	Autopsy	5 months	Cardia	Adenocarcinoma of cardia, in liver and lymph nodes	Esophagus, liver and peripancreatic lymph nodes and glands of hepatic hilus and lesser curvature		Died
Lapa	26	M	Autopsy	13 months	Pyloro-duodenal	Mucoid adenocarcinoma	Tumor in colon, duodenum; metastases in liver, gallbladder, pancreas, adrenals, kidney, suprarenal, hilus, mesenteric, lumbosacral glands		Died
Swartz, Swartz and Miller	41	M	Autopsy	6 months	Diffuse gastric cancer		Liver, adrenals and retropertitoneal, cervical, inguinal and axillary lymph nodes	Clinical diagnosis had been metastatic sarcoma	Died

TABLE 5.—*Cancer of the Stomach with Metastases in Patients with Acanthosis Nigrans—Continued*

Authors

Authors	Age	Sex	Verification of Tumor	Duration of Tumor	Site of Tumor	Classification of Tumor	Extent of Tumor and Metastases	Comment	Course
Bodenstein.....	38	F	Laparotomy	1 year	Stomach	Mesocolon glands in mesentery and along vena cava	Died
Küttner (case 3).....	54	M	Clinical picture	3 years	Stomach ?	Liver enlarged	Alive
Masson and Montgomery (case 3).....	38	M	No autopsy	20 months and over	Stomach	Carcinomatosis (including liver ?)	Died
Gordon.....	45	M	Operation	1 year	Stomach	Mucus-secreting sebaceous cancer of the stomach	Retroperitoneal and mesenteric lymph nodes	Alive
Herold, Kaufman and Smith.....	17	F	Operation	10 months	Lesser curvature	Colloid cancer of stomach in alveolar arrangement	Mass in the omentum, firmly attached to the abdominal wall, spreading along the gastrohepatic plexus and in the region of the celiac plexus and along the upper pole of the kidney; metastases in the preaortic nodes and along the colon	Died
Lipskerof.....	17	F	Clinical picture	Stomach ?	Liver enlarged	Alive
Flaskamp.....	23	F	Autopsy	4 months	Stomach	Alveolar arrangement of metastases	Ovary, uterus, portion of liver, pancreas, adrenals, lymph nodes in mesentery and celiac plexus glands and left supraclavicular	Alive; cachexia
Tsutsui.....	64	M	Clinical picture	7 months	Pylorus	Supraclavicular glands	Died
Matsuura.....	57	M	Clinical picture	14 months ?	Stomach ?	Supraclavicular glands	Alive
Sakiba and Saito.....	38	F	Clinical picture	Not reported	Stomach	Supraclavicular glands	Not reported
Hallopeau, Jeannelme and Meslay.....	60	M	Clinical picture	Not reported	Stomach	Supraclavicular glands	Not reported
Ssutejev and Talalajev; Ssutejev, Kiri.....	64	F	Clinical picture	Stomach	Supraclavicular glands	Not reported
Oastex and Fiebo.....	72	F	Clinical picture	Stomach	Supraclavicular glands	Not reported
Isaac.....	55	M	Operation; autopsy	Not given	Stomach	Supraclavicular glands	Died
Hess (case 1).....	33	M	Operation	About 3 years	Stomach	Metastasis shows glandular cancer	Supraclavicular glands; liver ?	Alive
Balassa.....	60	M	Clinical picture	18 months	Stomach	Melanotic tumor in esophagus; metastases	Died
Strandberg.....	72	M	Clinical picture	Not given	Stomach ?	Liver metastases	Alive
.....	55	F	Clinical picture	Not given	Stomach	Metastases in liver	Alive
.....	50	M	Roentgenogram	Not given	Stomach	Alive; worse

carcinoma of stomach with pancreatic metastasis). Herold, Kaufman and Smith's patient and the patient in Artom's case 1 showed alveolar gastric carcinoma.

Metastatic cancer in alveolar arrangement was found in the ovarian and other metastases of Flaskamp's patient with gastric cancer and cancer of the mesenteric

TABLE 6.—*Cancer of the Uterus in Patients with Acanthosis Nigricans*

Authors	Age	Verification of Tumor	Duration	Extent of Tumor and Metastases	Classification of Tumor	Course
Hellerström.....	58	Clinical picture	Over 1 year	Alive; unimproved
Bruck.....	51	Operation	Peritoneal metastases	Alive
Grosz.....	58	Autopsy	Several months	Retroperitoneal and inguinal lymph nodes	Medullary carcinoma (ulcerated)	Died
Pollitzer.....	42	Abdominal metastases	Died
Onozuka.....	64	No report *	At least 1 year	Alive
Hue.....	49	Operation	Several weeks	Tumor extending to vagina; pancreatic metastases (diabetes)	Died
Millan, Périn and Babalian; Millan	53	Hysterec-tomy	Several months	Cancer of body of uterus	Alive
Masson and Montgomery (case 1)	63	Operation	About 11 months	Tumor adherent to small bowel, bladder and broad ligament	Adenocarci-noma of body of uterus	Alive, skin worse

* Read only in abstract.

TABLE 7.—*Cancer of the Liver in Patients with Acanthosis Nigricans*

Authors	Age and Sex	Tumor	Verification of Tumor	Duration	Classification of Tumor	Course
Schröpl.....	61 M	Liver markedly enlarged	Clinical picture	Alive
Grace and Schwartz; Schwartz	46 F	Cancer of liver	Autopsy	About one year	Primary cancer of liver	Died
Tennessee and Leredde; Tennessee and Du Castel	42 M	Left lobe of liver indurated	Four to five months	Alive
Petrini de Galatz (case 3)	69 F	Clinical picture	Alive
Strandell.....	Autopsy	Primary cancer of liver	Died
Béron.....	55 M	Cancer of liver ?	Clinical picture	Lately	Alive; metastases in inguinal lymph nodes
Kobayashi.....	23 M	Cancer of liver ?	Clinical picture	No report	No report
Masson and Montgomery (case 2)	30 M	Multiple nodules in liver	Laparotomy	Eight months	Adenocarcinoma of liver (primary ?)	Died
Corrado.....	52 M	Cancer of liver	No report *	No report
Ravogli.....	? F	Cancer of liver	Died ?
Mazzanti (case 2)....	43 M	Cirrhosis of liver ?	Autopsy ?	Died
Mook and Drews.....	60 F	Cancer of liver	Operation	Two months	Adenocarcinoma of liver (primary ?)	Alive

* Read only in abstract.

glands and in the skin of Dubreuilh's patient, although in the primary cancer of the pylorus this arrangement was missing. The only evidence of a malignant neoplasm in Wild's case of acanthosis nigricans was a supraclavicular gland with

TABLE 8.—*Cancer of the Pelvis in Patients with Acanthosis Nigricans*

Authors	Age	Sex	Duration	Verification of Malignancy	Comments	Course
De Azua.....	62	M	Not given	Clinical picture	Acanthosis nigricans for 1 year	Alive
Schalek.....	55	F	8 months	No autopsy	Tumor in lower part of abdomen	Died
Thomae.....	34	M	(Lately)	Clinical picture	Tumor or metastases mostly in right side of pelvis	Alive
Tiefel.....	70	F	Not given	No autopsy	Metastases in inguinal glands	Died

TABLE 9.—*Abdominal Cancer in Patients with Acanthosis Nigricans*

Authors	Age	Sex	Duration	Verification of Tumor	Extent of Tumor and Metastases	Findings	Course
Pollitzer.....	62	F	1 month	No autopsy	Ascites "Carcinoma occultum"	Died
Gaucher, Photinos and Evangelou	51	M	Several months	Clinical picture	Inguinal and subclavicular glands	Orange-sized tumor below umbilicus	Alive
Halty, Correa Delgado and Volpé	2½	F	21 months	Operation; autopsy	Tumor extending to pelvis	Inoperable abdominal tumor	Died
Collan.....	41	F	Not given	Clinical picture	Abdominal tumor	Alive
Anderson.....	30	F	About 1 year	Unverified by laparotomy	Tumor ?	Alive
Burmeister.....	36	M	9 months	Clinical picture; unverified by autopsy	Died
Galloway.....	About 30	F	3 months	Clinical picture	Tumor in area of diaphragm	Alive
Masson and Montgomery (case ?)	37	F	4 years ?	Previous operations	Liver and spleen enormously enlarged, firm pancreas, enlarged lymph nodes in upper part of abdomen and along the vessels of back	Alive

TABLE 10.—*Cancer of the Rectum in Patients with Acanthosis Nigricans*

Authors	Age	Sex	Description of Tumor	Duration	Course
Elchhorst; Heuss.....	42	F	Large, ulcerated tumor	4 months	Alive
Little.....	60	M	Tumor of rectum	Not reported	Died

TABLE 11.—*Cancer of the Intestines in Patients with Acanthosis Nigricans*

Authors	Age	Sex	Verification	Duration	Course	Comments
Pollitzer.....	42	F	Clinical picture
Brito Foresti and Vignale	48	M	Operation	13 months	Died	At an earlier laparotomy ulcerations of the stomach and tumors of the intestines were seen

TABLE 12.—*Cancer of the Ovary in a Patient with Acanthosis Nigricans*

Author	Age	Sex	Duration	Tumor	Verification of Tumor	Metastases	Course
Soetomo.....	Late fifties	F	7 months	Carcinoma of the left ovary (inoperable)	Operation	Intestinal and peritoneal	Alive; cachexia

TABLE 13.—*Chorionic Carcinoma in Patient with Acanthosis Nigricans*

Author	Age	Sex	Duration	Verification of Tumor	Course
Spietschka.....	20	F	21 months after confinement; 18 months after operation	Operation	Alive; metastases

carcinomatous growth of the glandular type. The metastasis in Castex and Facio's case showed glandular cancer. In Tesseraux' case of gastric cancer the metastases of the liver and the lymph nodes near the solar plexus were of the glandular type. In the lower lobe of the right lung intra-alveolar growth of cancer with hemorrhagic purulent inflammation was seen.

Adenocarcinoma of the uterus was present in Masson and Montgomery's first case. Grosz found an ulcerated medullary cancer of the uterus. Hepatic nodules in Masson and Montgomery's second case consisted of adenocarcinoma of grade 1. The hepatic tumor of Mark and Drews's patient and of the dog with acanthosis nigricans described by Curth and Slanetz was an adenocarcinoma.

There was alveolar arrangement of the mammary cancer described in this paper, as well as in Freund's case of multiple nodules of the breast. In Matras' case of mammary cancer the metastasis in the liver presented a clear picture of alveolar cancer.

Scirrhus cancer of the stomach existed in Gordon's and in Takuwa's case. Two cancers of the breast were described as solid scirrhus cancers (Matras,

TABLE 14.—*Glandular Metastases (Site of Primary Cancer Unknown) in Patients with Acanthosis Nigricans*

Authors	Age and Sex	Metastases	Classification of Tumor	Duration	Comments	Course
Wild .	39 M	1. supraclavicular gland	Glandular cancer		.	Died, no autopsy
McDonald .	61 F	Postauricular and cervical glands	Small round cell carcinoma	1 year	..	Died; no autopsy
Archambault ..	54 M	Subclavicular gland	.		Gastric carcinoma suspected	
Markley. .	54 F	Subclavicular glands	.	2 months	Laparotomy and roentgenogram of chest negative	Allve (cachexia)
Syrkin and Niklsain.	27 M	Peritoneal and bronchial nodes; pancreas, lungs, adrenals, many bones	.	About 1 year	Stomach free	Died; autopsy

Vereinigung Rheinisch-Westphälischen Dermatologen). Tesseraux described the gastric cancer in his case as partly scirrhus, partly cylindric cell carcinoma. The mother of the patient in the first case I described suffered from colloid carcinoma of the rectum. Mucoid cancer was noted in Lapa's and in Gordon's case.

Sarcoma Associated with Acanthosis Nigricans.—Klotz and Rohdenburg found in their case of acanthosis nigricans spindle cell sarcoma of the colon with metastases in the lung, liver, kidney, mesenteric lymph glands and skin. Swartz's case of metastatic sarcoma of the liver showed at autopsy diffuse cancer of the stomach with metastases in the retroperitoneal and cervical lymph glands, adrenals and liver (Swartz and Miller). Wile reported a case of acanthosis nigricans with generalized lymphosarcomatosis. Masson and Montgomery's patient (case 8), aged 25, suffered from lymphosarcoma of the stomach which already at operation extended to the mesocolon and was associated with metastases to lymph nodes. Nicholas described a case of retroperitoneal lymphosarcoma in which widespread metastases in abdominal organs, lymph nodes, bone, cutis and subcutis were found at autopsy. Sánchez Covisa described a case of acanthosis nigricans with diffuse lymphosarcoma of the stomach and metastases. There was no histologic verification of the diagnosis of lymphosarcoma.

Theory of Epidermal Cancer Refuted.—Milian, Sauphar and Marceron reported that in a case of malignant acanthosis nigricans squamous cell cancer of a supra-clavicular gland occurred. They considered the neoplasm as of cutaneous origin. Since this possibility would be of fundamental importance, closer study of the evidence of the alleged cutaneous origin is indicated. The 31 year old woman had an intra-abdominal mass below the umbilicus. Enlargement of the supra-clavicular gland and other glands developed. She also had secondary syphilis. Acanthosis nigricans remained uninfluenced by arsphenamine. Later the patient complained of pain in the abdomen, and jaundice developed. She died after three months. At autopsy typical acanthosis nigricans was found. Large masses of sub-hepatic and prevertebral lymph nodes and secondary nodules in the liver were seen. There also was a soft mass in the stomach. In view of the clinical evidence there seems to be insufficient proof for assuming the presence of a cutaneous cancer.

Cases of Acanthosis Nigricans and Cancer in Dogs.—Acanthosis nigricans with cancer has also been observed in dogs. In collaboration with Dr. C. A. Slanetz, I described the case of a dog with acanthosis nigricans and multiple primary cancer of the liver (figs. 7 and 8). Although in 13 other cases of dogs with acanthosis nigricans no cancer was found (the completeness of all examinations necessary is open to doubt), the dog described by Schindelka showed medullary cancer of the thyroid gland with metastases to the lung, liver, kidney and lymph glands.

High Malignancy of Cancer.—It is evident from the tables that all cancers associated with acanthosis nigricans are highly malignant. They occur relatively frequently in the young (see table 2), and in old people no mitigation is seen. The mortality rate⁶ is high, and the duration is short. The average duration of cancer in cases of malignant acanthosis nigricans is eleven and ninety-five hundredths months.⁷ Even in old persons it is in no case longer than a few years. Early inoperability of the tumor is clearly evident from a study of the tables.

Küttner's, O'Leary's and Masson and Montgomery's suggestion to perform an exploratory laparotomy in all cases of acanthosis nigricans, if a malignant lesion cannot be detected otherwise, is reasonable, but its practical fulfilment seems problematic. There are cases on record in which an early laparotomy was done and in which no tumor was discovered. The 29 year old patient of Masson and Montgomery (case 6), nevertheless, died five months later under circumstances which suggested the presence of a neoplastic process. Another patient whose laparotomy revealed nothing (Markley) soon became cachectic, and an increasing swelling of the lymph glands below the clavicle became evident. A malignant tumor in the thoracic cavity was suspected, but the suspicion could not be substantiated by roentgen examination.

In reviewing the fate of 3 patients with acanthosis nigricans who had been subjected to exploratory laparotomy, O'Leary concluded: "In other words, in our efforts to cure acquired acanthosis nigricans by the early removal of abdominal cancer we failed."

The present case emphasizes the importance of mammary cancer in association with acanthosis nigricans. Cancer of the breast and cancer of the lung, as has been reported by Petrini de Galatz and Dore, would not have been detected by

6. Statistics on the ultimate outcome cannot be given because many authors did not publish any reports on mortality.

7. The figure for the duration of the cancer was computed from reports regardless of whether the patient was dead or still alive at the time of the report.

opening of the abdominal cavity. Neither would the tumor in Wanderer's case of acanthosis nigricans, in which roentgen examination suggested the presence of a tumor in the mediastinum.

In other cases, operations were carried out early but the tumor recurred or metastasized later (Masson and Montgomery [cases 3, 4, 7 and 8]; Spietschka [case 3]; Kuttner [case 2]; Castex and Facio; Bruck [carcinoma of uterus] Roffo and Iapalucci). In many cases (Flaskamp; Herold, Kaufman and Smith; Lapa; Bodenstein; Ostwald; Gordon; Halty, Correa Delgado and Volpé; Archangelskij; Pautrier; Masson and Montgomery [case 2]) the tumor was more extensive than had been anticipated, and surgical removal was impossible



Fig 7—Carcinomatous nodules in the liver of a dog with acanthosis nigricans ($\times \frac{1}{3}$) (Figures 7 and 8 were originally published with the article by Curth and Slanetz)

The fact that acanthosis nigricans many times made its first appearance only after operative removal of the tumor (Roffo and Iapalucci; Matras [gastric carcinoma]; Onozuka; Kreibich; Béron [case 3]; Gordon, Hodara; Montana; Kuttner [case 2]; Nicolas, Gaté and Lebeuf; Klein), after irradiation of the tumor (Hellerstrom) or after the two procedures combined (Matras [tumor of the breast], Masson and Montgomery [case 8], Vereinigung Rheinisch-Westphälischer Dermatologen) and that the patients rapidly got worse would also constitute a warning against expecting too much from an early operation. Nevertheless all examinations which would detect a tumor at the earliest possible moment and which would lead to its removal are strongly advocated.

ETIOLOGY OF ACANTHOSIS NIGRICANS

Previous Concepts of the Disease.—Role of Sympathetic Nervous System: Authors in the past have emphasized the prime importance of one of the factors, mostly of cancer. Darier was the first to state, and many authors have followed his conclusions (among them Wile; Wise; Couillaud; Montgomery and O'Leary; Masson and Montgomery) that when metastatic cancer presses on the sympathetic nervous system its fibers become irritated. His other hypothesis was that cancer

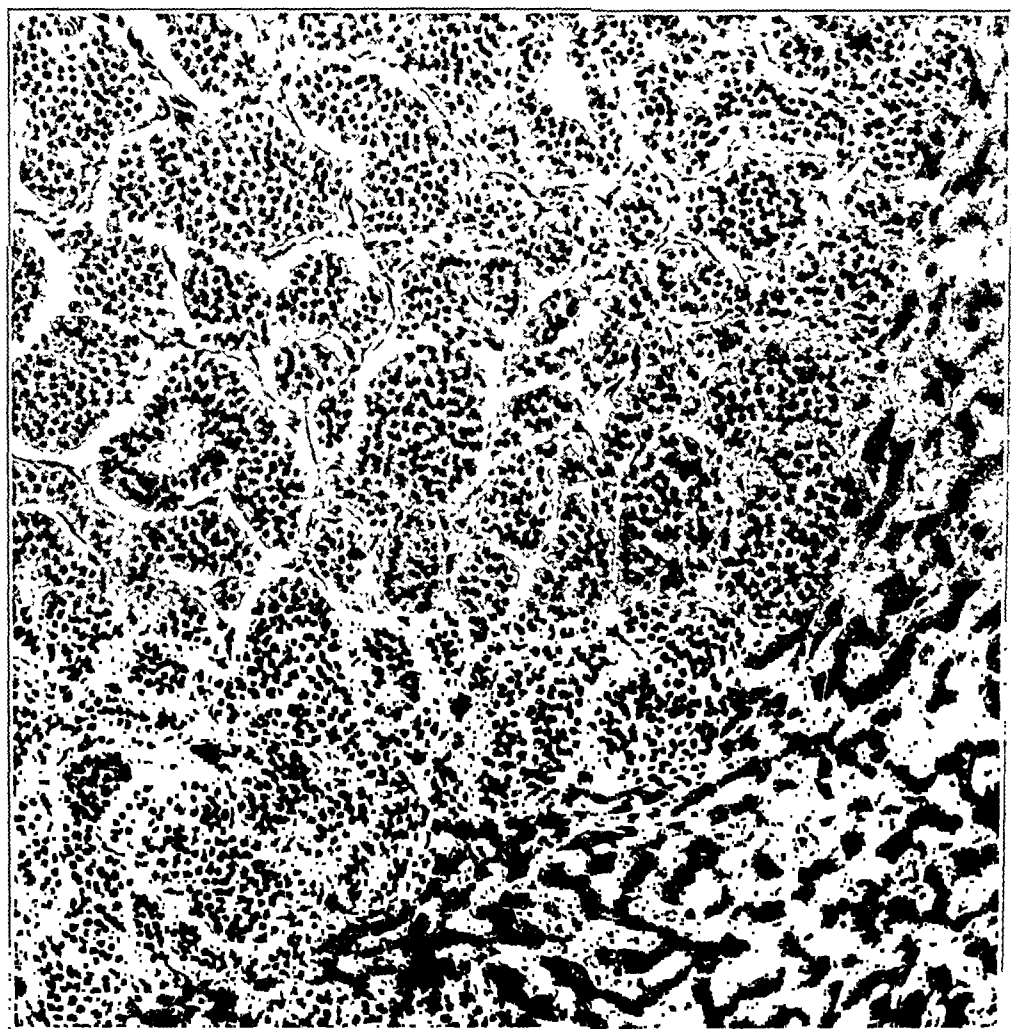


Fig. 8.—Cancer of the liver in a dog with acanthosis nigricans ($\times 100$). Normal hepatic tissue is seen at the extreme right.

causes an autointoxication which produces acanthosis nigricans. This toxin was supposed to act on the sympathetic nervous system (Bloch).

Role of Adrenals: The autopsy in the case described in this paper revealed that the left adrenal was invaded by tumor masses. Other authors who report involvement of one or both adrenals are: Swartz and Miller; Swartz; Shiga; Pollitzer; Perman (case 2); Darier (case 2); Petrini de Galatz; Ssutejev, Klirikow and Wainstein; Archangelskii; Nicholas; Dubreuilh (injection of lymphatics only); Flaskamp; Artom (case 1); Lapa; Kubo and Kosaka; Jakubson, Syrkin and Nikisain.

I agree with Halden Davis' statement that one of Addison's original cases is not an instance of Addison's disease but one of acanthosis nigricans. Case 8, in which the patient had typical cutaneous changes in the axillas (as suggested in a drawing) and around the umbilicus associated with a gastric carcinoma should indeed be regarded as a case of acanthosis nigricans with destruction of the adrenal gland. (Acanthosis nigricans was not yet recognized as a clinical entity in 1855.) In all these cases changes involving the adrenals were part of widespread metastases. The discovery of involvement of the adrenals seemed to establish the etiologic role of the sympathetic nervous system. Gordon, for instance, advocated this theory, although the autopsy in his case showed the adrenals to be free of cancer. There are also other cases of acanthosis nigricans with widespread metastases in which the adrenals were not involved in the cancerous process (Tesseraux; Arndt; Perman; Petrini de Galatz [lung tumor]; Scolari; Mazzanti; Toyama; Matras; Herold, Kaufman and Smith; Klotz and Rohdenburg). Perman rightly pointed out that the destruction of one adrenal capsule could not account for the complicated picture of acanthosis nigricans. Apparently, metastasis to the adrenals occurs in some cases of malignant acanthosis nigricans and not in others. It has no etiologic significance.

Endocrine Disturbances: Disturbances of the endocrine system have been extensively described in almost all reports of the benign type and even in a few reports of the malignant type of acanthosis nigricans. Most observers have agreed on their etiologic significance. In my first paper on acanthosis nigricans the etiologic role of the endocrine system was subjected to critical study. Theoretic considerations and actual records of cases speak against endocrine disturbances as a causative factor in acanthosis nigricans.

There is no one type of endocrine disturbance found in association with acanthosis nigricans. This observation is confirmed by recent reports which bring the previous review up to date.

Theodorescu observed amphotony and Goldschlag noted pluriglandular insufficiency. Yasuda and Ueki explained their patient's improvement following administration of solution of potassium arsenite (Fowler's solution) by the reduction of the epinephrine-like substances. Disturbances of the thyroid gland are frequently seen. One of Masson and Montgomery's patients (case 9) suffered from an adenoma of the thyroid gland. So apparently did the patient described in this paper. The patients of Behdjiet, Masson and Montgomery (cases 1 and 10). Perman (case 3) and Flaskamp had goiter. Strumitis purulenta was found at autopsy in Grosz' patient with cancer of the uterus. Cancerous metastases to the thyroid gland as well as to other parts of the body occurred in Schindelka's dog with acanthosis nigricans.

Reports on diabetes are rather frequent. It was seen in the case of Millán Gutiérrez, Ravogli, Hermans and Schokking, Pollitzer and Lawrence. Hue explained the occurrence of diabetes in his patient as due to pancreatic metastases. Miescher and Hellerström described familial diabetes. Becker and Obermayer observed decreased tolerance for dextrose. The case was later presented by Rothman and Henningsen with the diagnosis of acanthosis nigricans and a questionable Cushing's syndrome.

Diseases Coincidental with Acanthosis Nigricans: Acanthosis nigricans may be associated with diseases other than cancer. They are listed in table 15 and include congenital defects and various acquired diseases. None of them occur in any significant percentage of cases. Furthermore, the association of acanthosis nigricans with these various diseases lacks the close interrelationship which exists between acanthosis nigricans and cancer.

TABLE 15.—*Diseases Coincidental with Acanthosis Nigricans*

Authors	Disease	Benign or Malignant Acanthosis Nigricans	Comments
Mumford.....	Deformed head.....	Benign	
Kémeri.....	Dwarfs, enlarged thyroid gland, 1 member with supernumerary nipple	Benign	Family (5 members)
Miescher.....	Cutis verticis gyrata, dental deformities, hypertrichosis, juvenile diabetes, debility	Benign	Family
Moura Costa.....	Debility and congenital syphilis.....	Benign	
Mourek.....	Debility.....	Malignant	
Ellser.....	Debility.....	Benign	
Cavagnis.....	Debility.....	Benign	
Benedek and Csorsz.....	Idiocy and epilepsy.....	Benign	Acanthosis nigricans
Goldblatt.....	Debility.....	Benign	Acanthosis nigricans questionable
Dóczy.....	Idiocy.....	Benign	
Weiss.....	Cryptorchism.....	Benign	
Ottkhine.....	Double cryptorchism.....	Benign	
Mukai.....	Friedreich's disease.....	Benign	
Lange-Cosack.....	Achondroplasia.....	Benign	Family
Pautrier and Hugel.....	Nevi, not commonly associated with acanthosis nigricans; one nevus with transformation into neurocarcinoma	Benign	
Hodara and Behdjiet ..	Benign fibromatous nevi, covered with comedos	Benign	
Bernhardt.	Multiple nevi and keratoma palmare and plantare	Benign	Family
Kutznitzky	Keratoma palmare and plantare.....	Malignant	
Dowling and I reudenthal	Trichoepitheliomatous changes, also psoriasis	Benign ?	Acanthosis nigricans questionable
Hamdi and Reschad .	Budlike changes about the sweat glands, dermoid cyst	Benign	Acanthosis nigricans questionable
Jewsejeff and Posen .	Darier's disease	Malignant ?	
Theodorescu and Comsa..	Epidermolysis bullosa...	Benign	
Knowles.	Epidermolysis bullosa	Benign	
Foa...	Psoriasis.	Benign	Acanthosis nigricans questionable
Wolff..	Psoriasis	Benign ?	
Majocchi .	Urticaria.....	Benign	
Scarpa...	Urticaria.....	Benign	
Lehner.	Sclerema adultorum.	Benign	
Patrassi	Sclerema adultorum	Benign ?	Acanthosis nigricans questionable
Tzanek and Levy	Sclerema adultorum	Malignant ?	
Bernhardt	Bowen's disease, independent of the lesions of acanthosis nigricans	Benign	
Behdjiet ..	Lichen ruber acuminatus	Benign ?	
Rasch	Pityriasis rubra pilaris.... . . .	Benign	
Bahna, Braceras and Kaminsky	Pityriasis versicolor, acquired syphilis and obesity	Benign	
Milhan ..	Condylomata acuminata	Malignant	
Millan, Sauphar and Marcron	Syphilis, acquired	Malignant	
Bonnet.	Syphilis, acquired	Benign	Acanthosis nigricans questionable
Caussade, Lévy-Franckel and Juster	Syphilis, acquired	Benign	Acanthosis nigricans questionable
Touraine and Renault	Syphilis, acquired, and vitiligo	Benign ?	
Ingram	Syphilis, acquired, tumor in pharynx	Malignant ?	
Herold, Kaufman and Smith	Syphilis, acquired	Malignant	
Lawrence	Syphilis.....	Malignant	
Perman (case 3) .	Syphilis, acquired ?	Malignant ?	Acanthosis nigricans questionable
Perman (case 2)	Syphilis, acquired....	Malignant	
de Anduiza	Syphilis, acquired ?	Benign ?	
Mayo Clinic, and Masson and Montgomery (case 10)	Syphilis, congenital	Benign	
Crocker, R.	Syphilis of the central nervous system, goiter	Malignant ?	
Toyama.	Old serofulous abscesses.....	Benign ?	
Knowles, Sidlick and Ludy (case 2); Weldman	Miliary tuberculosis of omentum .. .	Malignant	
Solla Casalderey .	Tuberculosis of peritoneum... . .	Benign	
Mazzanti.	Tuberculosis of lungs	Benign	
Wollenberg	Tuberculosis of lungs	Malignant	Carcinoma of pylorus
Alkiewicz .	Tuberculosis cutis verrucosa	Malignant ?	
	Periarthritis nodosa	Benign ?	Acanthosis nigricans questionable
Matras	Parkinsonism	Benign ?	
S.	Acromegaly with tumor of hypophysis	Malignant ?	
P.	Alcoholism	Benign	
W.	Alcoholism and obesity	Benign	
Rapp.....	Obesity.	Benign	Family
Butterworth....	Obesity	Benign	
Sayer.....	Obesity	Benign	
Senear.....	Obesity; syphilis ?	Benign	
Becker and Obermayer	Obesity	Benign	
Jenneret.....	Aurantiasis palmarum.. . . .	Malignant	

Local Disturbances Preceding Cancer: Peptic and duodenal ulcer, constipation and vague gastric symptoms of long standing have been described in many cases of gastric carcinoma.

Perman stated that in the first of his 3 cases cancer developed secondarily in polyposis which had been present in the rectum and bladder. Gastric carcinoma was suspected on roentgen examination. Autopsy was not performed. The polyposis may perhaps be explained by involvement of the mucous membranes with acanthosis nigricans. Such was seen in the esophagus in the cases of Scolari, Tesseraux (also in nose, larynx and pharynx), Archangelskii, Ssutejev and Talalajev (also in rectum) and Toyama (conjunctiva) and was described as benign tumors of acanthosis nigricans in von Bergmann and Staehelin's "Handbook of Internal Medicine."

Activation of Acanthosis Nigricans.—In some cases acanthosis nigricans tends to subside after treatment of the tumor and then to reappear in full or even increased strength, with a recurrence or metastasis of the tumor. A study of this phenomenon suggests that some properties of the tumor may activate acanthosis nigricans, influencing it either directly or indirectly.

Improvement following nonspecific treatment, i. e., liver extract (Danbolt, Strandell), resection of the cervical ganglion (Mukai), arsphenamine (Bonnet) and thyroid extract (White; Rosenthal; Klotz and Rohdenburg; Knowles and Ludy; Yasuda and Ueki) shows that acanthosis nigricans can be influenced by methods which may not attack the accompanying cancer directly. A few cases of acanthosis nigricans (without cancer) also showed a limited response to these therapeutic measures.

If treatment of the tumor is attempted, the tendency to disappearance of acanthosis nigricans is not evident in all cases. It seems to depend on the extent to which the cancer (or carcinogenic substances or substances produced by the cancer) could be eliminated. These substances are certainly not the only determining factors, but they may play an activating role in the reproduction of the cutaneous lesion (Moncorps, Gaucher, Kyrle).

Role of Puberty.—In the benign form the same role of activation seems to be played by one of the sex hormones. In reviewing the literature I was surprised at the large number of patients with benign acanthosis nigricans in whom the cutaneous lesions of acanthosis nigricans appeared at puberty or in whom pre-existing lesions began to spread.⁸ It may also happen, as in the case of the young boy which I published in 1936, that symmetric acanthosis nigricans developed at puberty in a person who had had unilateral acanthosis nigricans since birth. Hellerström's observation of a man in whom acanthosis nigricans disappeared after castration seems to prove the same: One of the hormones of the sex glands is necessary for the reproduction of acanthosis nigricans. That sex hormones and substances produced by or related to cancers would play the same role (of activa-

8. Tolmach; Allen; Weiss; Frankenstein and Juliusberg (?); Artom (case 2); W. Jadassohn; Miescher; Hyde and Montgomery; Wertheimer; Boggs and Roblee; Sayer; Kinoshita; Butterworth; Wieder; Balina, Braceras and Kaminsky; Mayo Clinic; Ottkhine; Petrini de Galatz (case 1); Jacquet and Delotte; Jacquet; Frühwald (?); Pawlof; Chirivino; Mzareuloff; Goldschlag (?); Wile; Danbolt; Béron (case 2); Rasch; Brezovsky; Baliszka; Spietschka (case 1); Rille (cases 2, 3 and 4); von Leszczynski; Hodara and Behdjet; Conrad (?); Pechur and Čerkes (case 2); Rapp; Masson and Montgomery (case 10); Smith; Knowles, Sidlick and Ludy; Orol Arias and Landabure (acanthosis nigricans questionable); Behdjet (1932, case 2; 1934); Marziani (?); Jordan, Schamschin and Dobrow (case 2); Thomson; Senear.

tion) is not surprising in view of the importance of sex hormones as the cause of certain cancers (Lacassagne) and the close chemical relationship between sex hormones and some carcinogenic substances.

Importance of Cancer.—Endocrine disturbances 'apparently have no etiologic significance. The importance of pressure on the sympathetic nervous system due to abdominal cancers can be discounted, since some of the associated cancers are extra-abdominal. Furthermore, autopsies have failed to reveal involvement of the sympathetic nervous system, and there is a high incidence of the benign form of the disease, in which intra-abdominal changes are not present.

In studying the etiology of acanthosis nigricans one has to consider the benign type as well as the malignant. The histologic and clinical identity of the two types and the occasional transition from one to the other demand the same etiologic explanation.

The extremely high percentage of cancer associated with acanthosis nigricans and the parallel course of the two diseases are indicative of an intricate relationship between them. The study of malignant acanthosis nigricans cannot disregard cancer as an essential factor.

But does not the lack of cancer in the benign type, which represents one half of all cases of acanthosis nigricans, cast doubt on its etiologic significance?

The character of a genodermatosis, so much more obvious in benign than in malignant acanthosis nigricans, tends, indeed, to overshadow any other factor which may play a significant role in the origin of the disease.

Genetic Relationship Between Cancer and Acanthosis Nigricans.—Family Histories of Patients with Acanthosis Nigricans: Cancer can still be detected in cases of benign acanthosis nigricans. It is represented here by the involvement of a family member. Moncorps and Stihl have already stressed the frequent occurrence of carcinoma among the antecedents of patients with acanthosis nigricans. Table 16 gives data on cancer in the family histories of such patients. Among the immediate antecedents of patients with both the benign and the malignant form is found the same type of cancer (with the exception of cancer of the larynx [Matras]) which has been observed directly associated with malignant acanthosis nigricans. Cancers of the stomach, the liver, the uterus, the rectum and the breast have been reported. More data not only on the antecedents but also on the descendants and siblings of these patients will be needed in order to evaluate better the incidence of cancer in relatives of patients with acanthosis nigricans.

It cannot be denied that many antecedents are found without cancer, but it should not be overlooked that they may have died before cancer developed or that the phenotypic manifestation of cancer may have been influenced or even suppressed by other factors. In malignant acanthosis nigricans these opposing factors apparently are much less, or only temporarily, effective.

If we assume that the relationship between acanthosis nigricans and cancer is genetic, cancer keeps its significance even for a form of the disease in which it is absent from the clinical picture.

Furthermore, genetic relationship would explain the strange fact that two related factors occur in one instance combined in one person (malignant type), while in the other instance they occur dissociated in two separate but genetically related persons (benign type).

Any genetic relationship between two factors leads to the question of the heritability of each. Inheritance of acanthosis nigricans has been observed. Familial cases with involvement of as many as three generations have been noted.

In these cases acanthosis nigricans remained benign and did not assume the features of the malignant form (rapid spreading and a course parallel to that of an internal cancer).

Inheritance of cancer associated with acanthosis nigricans can be noted in several cases (table 16). This study will have to be made more complete and will have to include histories not only of antecedents but of descendants of patients with malignant acanthosis nigricans before definite conclusions as to the type of hereditary transmission can be drawn.

TABLE 16—*Data on Cases of Acanthosis Nigricans in Association with a Family History of Cancer*

Author	Acanthosis Nigricans		Family History of Cancer	
	Age in Years	Sex	Relative	Cause of Death
Baliszkaja ..	16	F	Father	Cancer of stomach
von Leszcynski	16	F	Father	Cancer
Asahi .	69	M	Father	Cancer of stomach
Wieder	10	F	Maternal grandmother	Cancer of stomach
Brünnauer .	23	F	Father	Branchiogenic carcinoma
Curth .	15	M	Mother	Colloid carcinoma of rectum at age of 36
Ogino ...	?	M	Father	Cancer of stomach
Liebner..	38	M	Mother	Carcinoma of breast
Tominaga and Harada	60	M	Paternal grandfather	Cancer of stomach
Radaeli	51	M	Father and brother	Cancer of liver
Becker and Obermayer; Rothman and Henningsen	11	F	Father	Branchiogenic carcinoma at age of 37
Guérault	39	F	Father and Sister of father	Intestinal (cancer ?) at 62
Grace and Schwartz .	46	F	Father	Cancer of stomach
	Primary cancer of liver			Cancer of rectum
Lapa	26	M	Father	Cancer of liver at 64
	Cancer of pylorus			
Mazzanti	60	M	Father	Neoplasm at 63
Darier . . .	30	M	Father	Cancer of stomach (?)
	Cancer of stomach			
Matras . .	52	F	Father	Carcinoma of larynx
	Carcinoma of breast			
Heuss, Eichhorst	42	F	Father and Sister	Cancer of stomach at 54
	Cancer of rectum			Cancer of breast at 36
Tiefel	70	F	Mother	Cancer of the uterus in the sixth decade
	Cancer of pelvis (?)			
Thomae ..	34	M	Father	Jaundice (tumor ?) at 68
	Tumor of pelvis			
Vellkanoff.....	50	M	Brother	Cancer
	Cancer of esophagus (?)			
Jordan, Schamschin and Dobrow	31	M	Mother	Cancer of stomach
	Cancer of stomach			

Glandular Cancers: The fact that glandular cancers are found is noteworthy in this connection. The hereditary factor is of more importance in glandular than in squamous cell cancer (Schinz and Buschke).

Chronologic Independence of the Two Diseases: In the case described in this article acanthosis nigricans seems to have appeared definitely six years (1932) before there was evidence of cancer (1938). This would be a long interval, but it is not the longest one on record, by far. We have already mentioned Freund's case of a 27 year old woman in whom cancer developed after acanthosis nigricans had been present for eighteen years. Artom described a 63 year old man in whom gastric cancer developed after he had been under observation for fifteen

years because of acanthosis nigricans. Van Leeuwen's patient, a 42 year old man, had had slowly progressive acanthosis nigricans for ten years before cancer of the stomach developed.

It seems that the two diseases are usually discovered at about the same time, or, since the early changes in the skin are more easily perceptible than the neoplasm, there is an apparently slightly earlier recognition of acanthosis nigricans. However, there are also reports of its appearance subsequent to the removal of the tumor (Tesseraux, Klein, Damblé, Hengstenberg, Lapa, Friedel, Doutrelepont, Pautrier, Soetomo, Hissard [a],⁹ Ostwald, McDonald [after manifestation of glandular metastases], Sánchez Covisa). Too great an interval between initial cancer and subsequent acanthosis nigricans would be improbable on account of the highly malignant character of the tumor.

I have dealt extensively with the problem of chronologic sequence of acanthosis nigricans and cancer in order to show that no definite rule about it can be set up. Sometimes acanthosis nigricans precedes cancer by a long time, sometimes by a short time. Frequently they start simultaneously. The onset of acanthosis nigricans rarely follows the manifestation of cancer. Conditions seem to vary from case to case, and one would have to conclude that neither disease is the primary one to which the other is a consequence. A genetic relationship between the two would not designate either disease to be the more important causative factor.

CRITERIA OF BENIGN AND MALIGNANT ACANTHOSIS NIGRICANS

If confronted with the problem whether a patient with acanthosis nigricans alone suffers from the benign type or from the type eventually associated with internal cancer, it is important to consider the following points:

1. The age of the patient at the onset of the disease is significant. The benign type will appear at birth or during the early years of life or at puberty. (Bernhardt recorded an exceptional occurrence in a family in which members of three generations showed the first signs of acanthosis nigricans at the age of 35.)

In cases of benign acanthosis nigricans the cutaneous lesions remain stationary and no cancer develops. The cases on record in which patients remained free from internal cancer for the longest period of time are those of Pautrier and Hügel, forty-four years (from the fifth to the forty-ninth year); Spietschka (case 2), 41 years (from the third to the forty-fourth year); Cavagnis and Giovanni, 28 years (from the third to the thirty-first year); Bérøn (case 2), 34 years, and Balina, Braceras and Kaminsky (from puberty to the thirty-third year). A sharp division of types, however, should not be based on age. In several cases malignant acanthosis nigricans has started at birth or in early childhood or shortly after puberty (table 2).

2. The duration of the cutaneous disease should be noted. We know that it is common to see acanthosis nigricans precede cancer by several months. But even a long freedom from cancer—the longest period on record is eighteen years in Freund's case—is no guarantee against association with it.

3. The distribution of the cutaneous disease is of importance. Malignant acanthosis nigricans occurs mostly in symmetric distribution. So does benign acanthosis nigricans, however, in the majority of cases. Unilateral distribution of acanthosis nigricans would be indicative of the neviform character of the disease, but would not completely rule out the later possibility of an associated cancer

9. Although Hissard and Périn, who discussed the case, did not make a definite diagnosis of cancer, symptoms suggestive of gastric carcinoma were already marked before onset of the changes in the skin.

(Halty, Correa Delgado and Volpé and Becker). Gougerot, Blum and Eliascheff's patient may have shown the extreme beginnings of acanthosis nigricans. In a 34 year old woman acanthosis nigricans of only the left axilla was accidentally found. An internal cancer was not discovered.

4. All reported familial cases of acanthosis nigricans have so far been of the benign type (Tolmach: son, mother, two maternal uncles and maternal grandfather; Kémeri: father, three daughters, one son; Sandbacka-Holmström: mother, two daughters; P. J. Schwarz: father and one sister with suspicious, one brother with definite, lesions; Barnhardt: three generations of a family; W. Jadassohn: mother and two children; Miescher (1921) and Hellerstrom (1933): father, one son, one daughter; Buri: two brothers; Lange-Cosack: acanthosis nigricans together with chondrodystrophia in two (not all) children, father and grandfather; Bloch: brother and sister).

5. The behavior of the skin appears to be a very important clue to the character of the disease. Spreading of the cutaneous lesions, if it does not occur at onset in childhood or at puberty, seems to be an ominous sign indicating the presence of cancer. The fact that in many cases cancer and acanthosis nigricans spread simultaneously would permit the conclusion that spreading of the cutaneous lesions is a bad prognostic sign in malignant acanthosis nigricans, even if the tumor still seems to be checked by therapy or if the case has heretofore been considered one of benign acanthosis nigricans.

6. The general condition of the patient should be studied most carefully. In the presence of acanthosis nigricans loss of weight, abdominal pain, jaundice, gastric anacidity, enlargement of the liver and edema have serious significance and deserve the greatest attention. Many of the cases reported as instances of benign acanthosis nigricans in the literature have not been observed long and thoroughly enough. A few notes have been published, in which authors who originally reported their cases as benign stated that their patients had later become ill with cancer or had died (Grace and Schwartz; Little; Burgess [in discussion on Dowling and Freudenthal]; Arndt [in discussion on Spietschka, 3]; Périn [in discussion on Hissard]). McDonald's patient with metastases, whose relatively good general condition was expressly noted, died shortly after the presentation (personal communication to the author).

CONCLUSIONS

Cancers associated with acanthosis nigricans possess no unique or remarkably new features. Analysis and comparison reveal the evident homology of their qualities. The cancers occur in various organs, are usually of the glandular type and are highly malignant. The preponderance of gastric cancer among the cancers associated with acanthosis nigricans corresponds to its high general incidence.

SUMMARY

A cancer of the breast in a woman with acanthosis nigricans proved to be highly malignant, like other cancers that have been associated with acanthosis nigricans. Benign and malignant acanthosis nigricans are identical. Previous concepts of the causation of acanthosis nigricans, such as those attributing it to disturbances of the sympathetic nervous system or of the adrenals or other endocrine glands, should be discounted and cancer considered the essential etiologic factor of acanthosis nigricans. In cases of malignant acanthosis nigricans some properties of the tumor may activate the cutaneous lesions. In the benign type the same role of activation seems to be played by one of the sex hormones. The

role of cancer in family histories of patients with acanthosis nigricans, the type of cancers that have been associated with acanthosis nigricans and the chronologic independence of acanthosis nigricans and cancer speak for a genetic relationship between acanthosis nigricans and cancer.

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SICKLE CELL DISEASE

WITH SPECIAL REGARD TO ITS NONANEMIC VARIETY

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Three years ago it was pointed out by one of us¹ that the disease known as sickle cell anemia might better be named sickle cell disease, because anemia, though the best known and most frequent sign of this disease, is not the essential and not the most dangerous one. If this fact is not realized, diagnostic mistakes with disastrous consequences may occur. It is assumed that circulatory stasis in the small blood vessels of the internal organs is the primary and the most perilous consequence of the sickle cell trait (sicklemia), which is an inborn and constitutional abnormality of the red blood corpuscles encountered so far almost exclusively in Negroes. Patients afflicted with this disease do not, as a rule, die from anemia but may die from circulatory stasis in some vital organs. Since the sickling phenomenon—that is, the distortion of the red blood corpuscles of the affected persons—is markedly enhanced, both in vitro and in vivo, by lack of oxygen and accumulation of carbon dioxide, any situation may become fateful that might bring about a diminution of oxygen supply. For this reason patients with sickle cell disease are poor medical and surgical risks. It is important to recognize this fact, as the disease is frequently not diagnosed, and patients are operated on unnecessarily because an erroneous diagnosis of appendicitis, gallbladder disease or some other type of acute abdominal disease has been made.

It has been estimated that about 7.5 per cent of North American Negroes exhibit the constitutional sickle cell trait. Even if this estimate is somewhat exaggerated, as we are inclined to believe, it is evident that the potential danger involved is by no means negligible, particularly as far as our armed forces are concerned. It has been demanded¹ that all Negro patients in both medical and surgical services be tested routinely for sicklemia. By this simple procedure many erroneous diagnoses could be avoided, such as rheumatic fever, rheumatic heart disease, polyarthritis, osteomyelitis, typhoid and other infectious diseases, cerebral disease, peptic ulcer, appendicitis and cholecystitis.² “It is particularly important that patients in surgical services should be so tested and that a positive result be regarded as calling for a revision of the indications for the proposed operation. Surgical treatment should not be given until the measures outlined have been instituted and carried out.”¹ Those measures aim at counteracting anoxemia and circulatory stasis. Routine testing for sicklemia is being done according to this

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1. Bauer, J.: Sickle Cell Disease, *Arch. Surg.* **41**:1344 (Dec.) 1940.

2. Diggs, L. W., and Bibb, J.: The Erythrocyte in Sickle Cell Anemia, *J. A. M. A.* **112**:695 (Feb. 25) 1939.

demand in the surgical department of Louisiana State University. For obvious reasons this practice should be carried on in the armed forces.

The present paper aims at supporting this demand. It will illustrate (1) that many cases of sickle cell disease are not diagnosed, and not even suspected, (2) that anemia is not necessarily present in patients with sickle cell disease. (3) that the cause of death may remain undetermined even at autopsy if the true nature of sickle cell disease is not given due consideration and (4) that persons with sickle cell disease represent biologic liabilities.

Since 1935 at the Los Angeles County General Hospital 6 patients have come to autopsy in whom "sickle cell anemia" was diagnosed by the pathologist. For 5 of these this diagnosis had not even been suspected by the clinicians. A similar experience has been reported by Wertham, Mitchell and Angrist.³ In 4 of their 5 cases the diagnosis was made only post mortem, by examination of the organs and blood.

REPORT OF CASES

CASE 1.⁴—James W., a 24 year old Negro, was admitted to the hospital on March 6, 1936. All his life the patient had had vague pains in the joints and bones which came on suddenly and disappeared spontaneously. He was first admitted to the hospital in 1928 complaining of pain in the right leg and in the jaw. Syphilitic periostitis was diagnosed, but the Wassermann reaction proved to be negative. In 1930 the patient was hospitalized because of dull, aching pain in the left hip. Roentgenograms showed changes suggestive of Perthes' disease or of tuberculosis of the hip joint but characteristic of neither. A series of roentgenograms taken throughout the various periods at the hospital were inconclusive. They showed a "local area of cystic degeneration, cause undetermined." The blood count in 1930 was as follows: red blood cells 5,150,000, white blood cells 6,500 and polymorphonuclear neutrophils 78 per cent. The smear was reported to be normal.

In the succeeding years the patient was admitted to the hospital twice for acute abdominal complaints. Both times he refused operation and recovered spontaneously.

On Aug. 15, 1933, a biopsy of the left hip was done. It showed macroscopically "marked thickening of synovia and a small amount of caseous-like material, giving evidence grossly of tuberculosis." This, however, was disproved by the microscopic study: "Sections show extensive fibrosis, areas of chronic inflammatory reaction with no evidence of tuberculosis. Some areas show many plasma cells."

On Aug. 30, 1935, the patient suddenly became ill with sharp pain in the epigastrium, followed by severe and continuous generalized abdominal pain. He vomited several times. Diagnosis of possible ruptured ulcer was made, but the patient refused an operation and recovered after several days. At this time the hemoglobin was found to be 90 per cent, the white blood cells 8,100 and the polymorphonuclears 76 per cent.

The last admission was for pneumonia, which was fatal two weeks after onset.

Autopsy.—Autopsy was performed on March 9, 1936, by Dr. J. P. Fitzgibbon. The patient was a well developed and well nourished Negro man. There was a scar, apparently of an old ulcer, over the anterior surface of the left leg near the ankle and a healed surgical scar over the left hip. On the epicardial surface there were fine splinter-like petechial hemorrhages. The myocardium was somewhat flabby and light brownish red. The aorta was normal. Pneumonia of the right lower lobe was apparent. The digestive system appeared normal. Particularly there was no evidence of the existence, past or present, of peptic ulcer. The liver weighed 1,700 Gm. and was dark purplish maroon. The spleen weighed 550 Gm. Several infarctions were to be seen. The lymphoid tissue of the mesentery was hyperplastic. The urinary and genital tracts were essentially normal. The adrenals were small and firm and appeared essentially normal.

The head of the femur appeared to have been destroyed by processes of roughening of the articular surface. The neck of the femur showed alternate areas of bone destruction and proliferation with osteophytes. The shaft of the femur itself at its cross section showed considerable cortical thickening and extreme narrowing of the marrow cavity, so that there was

3. Wertham, F.; Mitchell, N., and Angrist, A.: Brain in Sickle Cell Anemia, Arch. Neurol. & Psychiat. 47:752 (May) 1942.

4. This case, which is included by permission, is to be published in more extended form as a separate report by Drs. J. P. Fitzgibbon and R. A. Carter.

only a thin line of light brown marrow substance left. The sternum was followed across and the marrow appeared light brownish red and was essentially normal.

Microscopic Examination.—The fibers of the heart appeared of normal size. Under low power increased cellularity was especially pronounced around all the small vessels. There were no large scars. Definite sickled cells were in the capillaries. The alveolar walls of the lungs were not easily identified, but the alveolar spaces were crowded with polymorphonuclears and some macrophages and fibrin. The bronchial epithelium was normal. Another section showed alternating areas of alveoli filled with polymorphonuclears, macrophages and areas of necrosis in which the remains of alveolar structure could usually be seen. The vessels in these parts of the section particularly were packed with oat-shaped cells. The central areas of the liver were packed with oat-shaped and sickle cells, as were the sinusoids. The hepatic cells themselves were fairly intact. The triads contained some extra round cells and a large number of cells of the myeloid series, mostly polymorphonuclear, and there were a few collections of these cells in the lobules themselves. About half of the section of the spleen showed fairly normal-appearing malpighian bodies in the pulp, which was intensely packed with abnormal red cells, although the normal splenic structure was destroyed. The rest of the section was pale and made up of fibroblasts scattered in a background of broken-down red cells. The vessels were packed with sickle cells and fibrin. The line of demarcation was sharp. In the kidney glomerular tufts were congested here and there with red blood cells, as were the vessels in the region of the convoluted tubules, which were normal. The vessel walls were not remarkable. There were no inflammatory foci. The glomerular centers were hyperplastic, and the vessels were congested. There was considerable replacement in one part of the connective tissue, possibly due to an old infarction. Two sections of bone showed trabeculations of the cortex extending entirely through the medulla to the other surface of the cortex. The medullary tissue was enclosed in islands between the bone trabeculae. There were excessive numbers of myeloid series in all stages of development in the medulla.

The anatomic diagnosis was sickle cell anemia, lobar pneumonia of the right lower lobe, splenomegaly with infarctions and osteosclerosis of the left femur, with destruction of the left hip joint.

Comment.—This case is instructive for the following reasons: The history and course of sickle cell disease are typical as far as pain in the bones and joints and acute abdominal crises are concerned. Anemia, however, was absent at a time when marked structural changes of the skeleton were evident and an acute abdominal crisis occurred. The changes in the bones could not be interpreted because the sickling phenomenon had not been looked for. The correct interpretation of the roentgenograms was not possible before the autopsy and particularly before the microscopic examination had revealed the characteristics of sickle cell disease. The term sickle cell anemia is not justified in such a case because pathologic changes due to sickle cell disease were present when anemia did not exist, and because even at autopsy no indication of anemia was found. The dark purplish maroon color of the liver is not in accord with anemia. Splenomegaly with infarcts, hyperplastic lymph nodes in the mesentery, the changes of the skeleton and the engorgement with distorted red blood corpuscles of the vessels of the lung, liver and spleen proved the case to be one of sickle cell disease apparently without anemia. Sicklemia had caused a serious disease but not anemia.

CASE 2.—Eloise A., a 26 year old Negress, was admitted to the hospital on July 24, 1935, complaining of severe pain in the back on both sides, particularly on the left, chills, fever and vomiting for four hours. Her past history and family history were irrelevant. The patient was well developed and well nourished. Her temperature was 98.2 F., the pulse rate 96 and the respiratory rate 44. There were no abnormalities in the lungs or heart. There was generalized rigidity of the abdomen, most marked in the left lower quadrant, and extreme tenderness of the whole abdomen. The patient had stiffness of the neck and generalized muscular tenderness, especially of the muscles of the extremities. The urine contained traces of albumin but no sugar. There were 10 white blood cells per high power field. The Gram stain showed numerous gram-negative rods but few gram-positive cocci. The white blood cell count was 9,500, polymorphonuclears 86 per cent and lymphocytes 14 per cent, and non-protein nitrogen 16 mg. per hundred cubic centimeters. Phenolsulfonphthalein appeared in the urine in four minutes—45 per cent in one-half hour, 15 per cent in one hour. Roentgeno-

grams of the kidneys, ureters and bladder indicated normal conditions. The patient died after three days of severe pain. A clinical diagnosis was not made.

Autopsy.—Autopsy was performed on July 27 by Dr. L. J. Tragerman. The skull and central nervous system, heart and aorta, respiratory system and digestive system were essentially normal, except for moderate congestion of the lower lobes of the lungs. The liver weighed 1,590 Gm., was mottled, mahogany brown and of slightly softer than average consistency. The cut surfaces were reddish brown. The spleen was greatly enlarged, weighed 620 Gm. and was dark reddish brown. The cut surfaces were dark mahogany brown and moderately firm. Malpighian markings were totally obscured. There was no enlargement of cervical, axillary and inguinal lymph nodes. The left kidney weighed 170 Gm.; the capsule stripped easily from a smooth, lightly ecchymotic, brown surface; there were three small areas of old infarction visible on external examination. The cut surface was apparently normal, except for many punctate hemorrhages throughout. The right kidney weighed 165 Gm.; the capsule stripped easily from a smooth, brown surface, and surfaces of the sections were apparently normal. Pelves and ureters were normal. The urinary bladder was normal, except for slight ecchymoses in the region of the trigone. There was marked hyperemia of the uterus, tubes and ovaries. The adrenals were apparently normal. The skeletal system also was apparently normal.

Microscopic examination of sections of the liver and kidneys showed sickling of the red blood cells: cloudy swelling, tubular degeneration, acute glomerulitis and infarctions of the kidneys; cloudy swelling of the liver with periportal infiltration (round cells and polymorphonuclears); hemorrhagic splenomegaly, and pulmonary edema.

The anatomic diagnosis was hemorrhagic splenomegaly, punctate hemorrhages of the kidneys and sickle cell anemia.

The probable and official cause of death was not determined by autopsy (Dr. O. M. Stewart).

Comment.—Anemia, particularly sickle cell anemia, had not been suspected clinically, and therefore a red cell count had not been done. Even at autopsy there was no evidence of anemia. Yet the hemorrhagic splenomegaly and the microscopic evidence of sickled erythrocytes were proof of sickle cell disease. The important fact is that the pathologist was unable to determine the cause of death and to explain the clinical symptoms. Rightly he did not consider the pathologic changes of the kidneys a causal factor of death. Clinically there was no evidence of renal functional failure. As long as the true nature of the disease—that is, the vascular engorgement with disfigured erythrocytes resulting in circulatory stasis—had not been recognized, both the clinical picture and the cause of death must have remained mysterious. Whether or not such a circulatory stasis could have been found in the small vessels of the splanchnic area and of various muscles cannot be established, as it had not been looked for. Yet we venture to guess that circulatory stasis was present, because such a finding would be in accord with our conception of sickle cell disease and would explain the acute abdominal symptoms, the stiffness of the neck, the muscular tenderness and the eventual death.

CASE 3.—Margret M., an 80 year old Negress, was admitted to the hospital on Aug. 16, 1935, one week before her death. She was too enfeebled and later too stuporous to give a history. She was incontinent of urine and feces and had a large sacral decubital ulcer. Physical examination gave essentially normal results. The blood pressure was 140 systolic and 85 diastolic, nonprotein nitrogen 60 mg. and creatinine 1.6 mg. per hundred cubic centimeters. No blood count was done. The clinical diagnosis was generalized arteriosclerosis.

Autopsy.—Autopsy was performed on Aug. 26, 1935 by Dr. E. J. Joergenson. The following changes were revealed: greatly atheromatous and tortuous arteries at the base of the brain, some hydrocephalus and slight atheromatosis of the aorta and of the coronary arteries. The heart, lungs and digestive tract were essentially normal except for old pleural and peritoneal adhesions. The liver was brownish black on the cut surface. The spleen was atrophic and fibrous, and its weight was only 25 Gm. The lymphoid tissue of the periaortic lymph nodes appeared to be somewhat increased. The urinary system was normal, and the kidneys had a smooth brown surface. The bone marrow of ribs and vertebrae appeared red.

Mounts of the venous blood revealed definite sickling after standing for several hours.

Microscopic examination of the spleen showed marked hyalinization of the capsule and septums. The malpighian arteries were mostly obliterated. There were oat-shaped red blood corpuscles in the pulp.

The official cause of death was declared to be sickle cell anemia (Dr. C. H. Francis).

Comment.—Again anemia had not been suspected, and therefore a blood count had not been done. Anemia was not proved at autopsy either, as can be concluded from the color of the liver and kidneys. Death was sufficiently explained by the arteriosclerosis. The patient had, however, sickle cell disease with the characteristic changes of the spleen, the hyperplastic abdominal lymph nodes and the red bone marrow. This case illustrates the known fact that persons with sickle cell disease may occasionally escape the hazards of their unfortunate constitution and reach old age.

CASE 4.—Leah S., a 20 year old Negress, was admitted to the hospital on April 22, 1935. She was in the fifth month of pregnancy and entered the hospital because of dyspnea, pain in the chest and cough with raising of blood-tinged sputum for four weeks. Her temperature was 101 F. and her pulse rate 120. The scleras were icteric. Dulness, decreased breath sounds and crepitant rales with increased tactile fremitus over both lower lobes of the lungs were found. The heart was normal and the blood pressure 115 systolic and 70 diastolic. The uterus was enlarged. The liver and spleen were not palpable.

The urine was negative for albumin and sugar. The red blood cell count was 1,920,000, hemoglobin 35 per cent, color index 0.92, white blood cells 26,000, polymorphonuclears 87.5 per cent, monocytes 9 per cent and lymphocytes 3.5 per cent. The red cells were predominantly large and relatively hypochromic. The platelets appeared normal.

The clinical diagnosis was bilateral bronchopneumonia and macrocytic anemia of pregnancy.

Autopsy.—Autopsy was performed by Dr. L. J. Tragerman on April 22, 1935. Multiple infarcts in the lower lobes of both lungs were due to embolisms originating from thrombophlebitis of the uterine veins. The body of the uterus was symmetrically enlarged, and its cavity was filled with normal attached placenta and an amniotic sac containing well developed twins about 20 cm. in length. The cut surface of the liver was pale brown with normal markings. The spleen was unusually small, measuring about 3 cm. in length, weighing less than 25 Gm. and containing an old infarct. The bone marrow in the lower end of the femur and in the middle of the tibia was bright red.

The official cause of death was declared to be pelvic thrombophlebitis with multiple pulmonary infarcts and macrocytic anemia of pregnancy (Dr. H. B. Haining).

Microscopic section of the spleen showed sickle cells in the reticulum and severe siderofibrosis.

Comment.—This case does not require particular comment. There were anemia and pregnancy. Yet, whether the anemia did not exist before the pregnancy was not known. In spite of the icteric scleras, the sickling phenomenon had not been looked for. Whether the case should be classified as macrocytic anemia of pregnancy or as sickle cell anemia with pregnancy cannot be decided. That not only sicklemia but sickle cell disease had been present was proved by the characteristic appearance of the spleen.

CASE 5.—Laura M. de H., a 14 year old Negress, was admitted to the hospital on August 21, 1940 in coma and died thirty minutes after admission, in spite of emergency treatment. The only available information concerned her severe vaginal bleeding for the past month. Two similar episodes had occurred in the past four years. The patient was extremely pale. Her respiration was gasping and stertorous, and the rate was 15 per minute. No radial pulse was palpable. The apical rate was 80 and the rhythm was regular. There were moist rales at the bases of both lungs. Pelvic examination revealed the hymenal ring intact and the cervix closed and firm, with oozing of a moderate amount of serosanguineous fluid. The corpus uteri was of average size, at the left and anteriorly. The adnexa were normal.

Autopsy.—Autopsy was performed on August 21 by Dr. S. D. Leo. The body was that of a well developed and well nourished, somewhat obese mature Negress weighing 72.5 Kg and measuring 150 cm. in length. There was excessive hair on the side of the face and over the entire mid-region of the back. No icterus was present, but there was pronounced pallor of all visible mucous membranes. The breasts were well developed, with a large amount of glandular tissue. There were striae distensae over the thighs and breasts. No

gross abnormalities were observed of the skull, central nervous system or cardiovascular system except for extreme anemia. The level of the right side of the diaphragm was at the third rib, that of the left side at the third interspace. Each lung weighed 250 Gm. The thymus appeared pale and weighed 46 Gm. after removal of the parathymic fat. Otherwise the organs of the chest, the digestive and hepatic system, spleen and lymphatic system and urinary tract displayed no gross abnormality except anemia. Neither was there any gross abnormality of the thyroid, parathyroids, adrenals and pituitary gland. The bone marrow of the sternum and of the skull appeared extremely anemic. The uterus was about one and one-half times normal size, and the endometrium was definitely hyperplastic and cheeselike in consistency, with blood-tinged areas and blood clots. The ovaries were about two and one-half times normal size and rather soft. The color of the external part was white with a tinge of blue. The cut surfaces of both ovaries revealed numerous small follicular cysts, none larger than 3 mm. in diameter. In addition, the left ovary contained a large cyst, about the size of a small grape, which was filled with red fluid blood.

Postmortem examination of the blood revealed: hemoglobin 1.2 Gm. (7.4 per cent), red blood cells 320,000, color index 0.82, white blood cells 21,600, a reduced number of platelets, polymorphonuclears 36.5 per cent, lymphocytes 58 per cent, mononuclears 1.5 per cent, metamyelocytes 1.5 per cent, myelocytes 2.5 per cent and 11 normoblasts per 200 white blood cells. Sick cell preparation showed typical sickling of red cells. The Wassermann reaction was negative.

Microscopic examination showed great endometrial hyperplasia in the proliferative phase with hemorrhages; multiple maturing ovarian follicles in all stages of development and numerous follicular cysts but no corpus luteum formation, and hyperplasia of red and white elements of the bone marrow. In the spleen there were areas of hemorrhage around some small malpighian follicles. The capsule and trabeculae were normal. Many deformed erythrocytes, some sickle shaped, were found in the spleen and liver.

The official cause of death was declared to be endometrial hyperplasia with hemorrhage and sickle cell anemia (Dr. Gertrude Finkelstein).

Comment.—This case is of interest for the following reasons. There is no proof of sickle cell anemia, and scarcely of sickle cell disease. The fatal anemia resulted from the uterine hemorrhage, and this was due to the follicular cystic degeneration of the ovaries with failure of corpus luteum production. It was a typical case of fatal postpubertal hemorrhage. The absence of icterus is not in accord with sickle cell anemia. The anemia was obviously posthemorrhagic, not hemolytic, in nature. The microscopic changes in the spleen might suggest the very first stage of circulatory stasis due to a beginning of sickle cell disease.

The combination of the sickle cell trait (sickleemia) with the cystic degeneration of the ovary, however, deserves attention. The sickle cell trait is a constitutional abnormality that may or may not result in a serious disease. It is indicative of at least one abnormal gene representing a definite morbid predisposition (to sickle cell disease). As has been pointed out elsewhere,⁵ it is to be expected that not infrequently this abnormal gene is only one among many other pathologic genes; in other words, that sickleemia is one of numerous constitutional deviations of a person from the normal average. In the paper just quoted,¹ several examples were reported of such a multiple genotypic deviation called "status degenerativus," including, among others, the sickle cell trait. It is important to recognize that the well defined genopathy predisposing to sickle cell disease may be indicative of farther reaching chromosomal abnormalities known as status degenerativus.

In our case such a status degenerativus is evident from the following findings proving or suggesting constitutional (genotypic) abnormalities: cystic degeneration of the ovaries, hyperplastic thymus weighing 46 Gm., the abnormally high level of the diaphragm, lymphocytosis of 58 per cent among 21,600 white blood cells, hypertrichosis and mild obesity. That the diaphragm may be found at a higher level in persons with status thymolymphaticus was emphasized by Byloff⁶

5. Bauer, J.: *Constitution and Disease: Applied Constitutional Pathology*, New York, Grune & Stratton, Inc., 1942; footnote 1.

6. Byloff, K., cited by Bauer.⁷

in 1914. It is, however, nothing but a degenerative stigma mostly associated with other genopathies.⁷

CASE 6.—Jennie H., a 33 year old Negress, was admitted to the hospital April 16, 1940. She was first seen in the internal medicine clinic in October, 1936. She complained of weakness during the preceding six months and of shortness of breath on exertion for several years. Her last menstruation was in 1933. Diagnosis of sickle cell anemia was made. The red blood cell count was 3,480,000, hemoglobin 54 per cent, color index 0.79, white blood cells 12,550, polymorphonuclears 48 per cent, lymphocytes 48 per cent, eosinophils 3 per cent and monocytes 1 per cent. There were pronounced poikilocytosis, anisocytosis and sicklemia. The patient was treated with liver extract but responded only slightly. By December 1937, her hemoglobin had risen from 54 per cent to 84 per cent. She was admitted to the hospital on Jan. 9, 1938, with symptoms of an acute abdominal condition and recovered without surgical intervention. One blood transfusion was tolerated without reaction. She was discharged on January 22. Liver therapy was continued, but the patient was readmitted on June 21 and October 10, and again on April 16, 1940, because of increasing anemia. Several transfusions were given each time. One severe reaction occurred in June 1938. On May 1, 1940, the hemoglobin was 50 per cent and the red blood cells 2,710,000 with marked sickling. Another direct transfusion was done. The next day the patient had a temperature of 102 F., albuminuria and severe backache. She died two days after the transfusion. The physical examination was reported as giving essentially normal results except for the icteric tinge of the scleras and a systolic murmur at the apex of the heart. The urine was normal and the Wassermann reaction negative.

Autopsy.—Autopsy was performed on May 3 by Dr. B. E. Levine. There was an extensive subdural hemorrhage covering the major portion of the dorsolateral surface of the right cerebral hemisphere which evidently had caused the death of the patient. The aorta showed minimal subintimal cholesterol deposits. There was pulmonary edema. The gallbladder contained four irregular pigmented stones, the largest of which measured 4 mm. in diameter. The spleen was found with difficulty and was extremely atrophic. It weighed 2.5 Gm. and measured 3 by 1 by 0.4 cm. There was a generalized enlargement of the lymph nodes, including the tracheobronchial, abdominal and even epitrochlear. The lymph follicles of the stomach and the solitary follicles of the intestines were hyperplastic. The thymus was greatly enlarged and weighed 65 Gm., and it had little perithymic fat. The bone marrow of the sternum, vertebrae and femur appeared red and hyperplastic. Pubic hair was somewhat scanty. In the right anterior axillary line overlying the costal margin was an irregular, ovoid dark brown birthmark measuring 4.5 by 3.5 cm. The circumference of the pulmonary artery was 8 cm., that of the aorta 6.5 cm. The left lung presented an anomaly in that only a single lobe was demonstrable. Within the cortex of the left kidney was a smooth-walled cyst 1 cm. in diameter. The uterus, tubes and ovaries as well as the thyroid, pituitary and adrenals appeared to be normal.

Microscopic examination showed the typical hemosiderotic, hyalinized, fibrous spleen with only a few areas of lymphocytes and congested vessels. The sinusoids of the liver were greatly dilated and filled with bizarre-shaped red blood cells. The hepatic cords were thinned and atrophic, many cells showing cloudy swelling. Extreme vascular congestion with oat-shaped and sickled erythrocytes was found in the kidneys, pancreas, lungs and pituitary. Tubular necrosis and hemosiderosis of the kidneys were apparent.

The official cause of death was declared to be massive subdural hemorrhage after blood transfusion and sickle cell anemia (Dr. R. M. Hill).

Comment.—Among the 6 reported, this was the only case in which the diagnosis sickle cell anemia had been made clinically. The clinical picture and course as well as the underlying pathologic changes observed at autopsy were typical. Severe reactions and even death of a patient with sickle cell disease after a blood transfusion have been reported previously.⁸ Such a reaction may occur even if previous transfusions have been well tolerated.

This case again illustrates a status degenerativus: status thymicus, the abnormality of the left lung, the amenorrhea and scanty pubic hair, the birthmark, the

7. Bauer, J.: *Konstitutionelle Disposition zu inneren Krankheiten*, ed. 3, Berlin, Julius Springer, 1924.

8. (a) Tomlinson, W. J.: *Studies of Sicklemia Blood*, *Am. J. Clin. Path.* **11**:835 (Nov.) 1941. (b) Wintrobe, M. M.: *Clinical Hematology*, Philadelphia, Lea & Febiger, 1942. (c) Bauer.¹

lymphocytosis of 48 per cent among 12,550 white blood cells and the relative preponderance of the pulmonary artery as compared with the width of the aorta may be considered as signs of an abnormal constitution. The generalized hyperplasia of the lymphatic tissue is frequent in sickle cell disease¹ and probably a direct consequence of the disease rather than a constitutional stigma. Gallstones and solitary cysts in the kidneys are too frequent to permit of any evaluation in our case.

CASE 7.—Finally the history of a case may be referred to which fortunately did not come to autopsy but which nevertheless illustrates several essential facts: (1) that a person of white race without known Negro ancestry may be subject to sickle cell disease; (2) that sickle cell disease may not be suspected in a patient presenting the clinical picture of an acute abdominal condition, and (3) that a severe condition may result from sickle cell disease without marked anemia.

The history of this case will be reported extensively by Drs. Canby, Carpenter and Ellmore from Southern California University Medical School.

It is the case of a 19 year old white youth born of Sicilian parents who was operated on when a diagnosis of torsion of the spleen on its pedicle was made. Splenomegaly of a considerable degree was found with an extensive area of fibrinous perisplenitis. There was no torsion of the spleen or gross evidence of splenic vein thrombosis, and the liver appeared to be normal. Splenectomy was done.

After the operation marked sickling of the red blood cells was found, and the microscopic examination of the spleen revealed the typical picture of sickle cell disease. There was practically no anemia, but the icterus index was found to be 44.

Comment.—There exist only a few reports of sickle cell anemia in persons of the white race. According to Wintrobe^{8b} there are now reports of 7 instances of sickle cell anemia in white families which seem unchallengeable. Lewis⁹ recognizes only 3 instances in pure Caucasians and considers even these as questionable because of the possibility of admixture of Negro blood in past generations. This view is shared by Ogden.¹⁰ In fact, almost all the cases of sickle cell anemia observed in persons of the white race were in patients of Greek, Italian or Sicilian stock. Two more cases in white children of southern Italian descent were reported recently.¹¹ The patient in case 7, too, was born of Sicilian parents. We agree with Morrison, Samwick and Landsberg¹¹ that search for the sickling phenomenon should be undertaken in all cases of obscure hemolytic disorders, even in white patients. The case to be reported by Canby, Carpenter and Ellmore, however, demonstrates that such a search should not be limited to patients with obvious anemia of hemolytic origin. This patient had only a negligible reduction of hemoglobin (12 Gm., 75 per cent) and a normal red cell count (4,750,000). Yet the icterus index was increased (44). Sickle cell disease without anemia may, therefore, occur also in persons of the white race and may cause a serious clinical picture. The clinical picture presented by this patient is the only possibly justified indication for splenectomy in sickle cell disease. The acute development of an extremely painful splenomegaly aroused the suspicion of a torsion of the spleen on its pedicle or of a thrombosis of the splenic vein. It can be assumed, however, that the patient would have recovered even without the operation.

The fact that the patient's parents and siblings did not have the sickle cell trait is at variance with the assumption that sickle cell anemia is transmitted by heredity as a simple dominant mendelian characteristic. It can hardly be surmised that the sickle cell trait of our patient was caused by mutation, since the occurrence of this trait in the white race is questionable.

9. Lewis, J. H.: *Biology of the Negro*, Chicago, University of Chicago Press, 1942.

10. Ogden, M. A.: Sickle Cell Anemia in the White Race, with Report of Cases in Two Families, *Arch. Int. Med.* **71**:164 (Feb.) 1943.

11. Morrison, M.; Samwick, A. A., and Landsberg, E.: Sickle Cell Anemia in the White Race, *Am. J. Dis. Child.* **64**:881 (Nov.) 1942.

COMMENT

When the material presented here is considered, reason dictates that to abandon the misnomer sickle cell anemia and to use the term sickle cell disease¹ is not only justified but imperative. Anemia is only one of the consequences and the most frequent and obvious sign of this disease. One does not call a cancer or a peptic ulcer resulting in anemia cancer-anemia or ulcer-anemia but designates it as cancer or ulcer with subsequent anemia. The question is not only one of academic terminology but also the highly practical one of the correct conception of the underlying pathologic anatomy and physiology. It is essential to have this conception in order to avoid erroneous diagnoses and treatments and to institute correct management. The main danger to the patient does not result from the anemia—this has also been emphasized by W. Schiller¹²—but from the circulatory stasis in various organs. Cases 1 and 7 prove that a serious impairment of health may occur in sickle cell disease without anemia.

We cannot agree with Wintrobe^{8b} when he considers the sickle cell trait "to be of little clinical significance" (p. 467) and when he says that "in association with the trait alone, neither anemia nor the above symptoms [i. e., symptoms suggesting acute abdominal disease, rheumatic fever, osteomyelitis or neurologic disorders] are produced." Our observations are not in accord with Wintrobe's claim that for the diagnosis of such a case sickling of the red blood cells is not sufficient but that sicklemia, anemia with active red cell regeneration, leukocytosis and bilirubinemia are necessary (p. 464). We subscribe, however, to his somewhat contradictory statement that "the difference between sickle cell anemia and the sickle cell trait may perhaps be only one of degree" (p. 467).

A person burdened with the constitutional sickle cell trait has one of the following chances:

1. He may have the constitutional sickle cell trait without any further consequences.

2. There may develop an actual sickle cell disease, as proved by the characteristic anatomic findings, chiefly in the spleen, but without noticeable impairment of health. Such a condition is not incompatible with the attainment of old age (case 3).

3. Actual sickle cell disease may develop, causing circulatory stasis in various organs and thereby producing abdominal or neurologic symptoms, pain of bones and joints and other manifestations of such an impaired circulation. Anemia is not a necessary sign, as demonstrated by cases 1 and 7.

4. A more or less severe anemia may develop as the leading sign of sickle cell disease. This is the full-fledged sickle cell anemia (case 6).

5. The sickle cell trait may be present and the patient may be on the verge of sickle cell disease or have an actual sickle cell disease but suffer from severe anemia of a nature different from sickle cell anemia (cases 4 and 5).

6. Having the sickle cell trait, whether or not resulting in sickle cell disease with or without anemia, he may become the victim of his constitutional biologic inferiority and succumb under circumstances which are innocuous to average normal people. The condition may be due to one of two factors:

- (a) The mechanism which facilitates the conversion of sicklemia into sickle cell disease or accelerates the progress of sickle cell disease may be set into action if a large number of red corpuscles are caused to sickle. This may be brought about by local or general anoxemia, which in turn may result from infectious-

12. Schiller, W., in discussion on Kobak, Stein and Daro,^{1*} p. 821

diseases, surgical procedures and other circumstances that are known to slow the circulation of the blood. Pregnancy also may be such a factor.¹³ The risk of blood transfusions has been mentioned.⁸

(b) Persons with the sickle cell trait may also have other constitutional abnormalities. In other words, they may be representatives of a "status degenerativus."¹⁴ Such a constitutional state has to be considered as a biologic liability, lowering the resistance and adaptive power. Our cases 5 and 6, as some other cases of sickle cell disease previously reported by one of us (J. B.),¹ are instances of a status degenerativus. We find a confirmation of our view by Wintrobe¹⁵: "Sickling of the red corpuscles may therefore be only one of several degenerative stigmas with which these individuals are burdened" (p. 467). Wintrobe reports the case of a 22 year old Negro with sickle cell anemia showing tower skull. He appeared younger than his stated age and was found to have bilateral hypoplasia of the terminal phalanx of the fourth finger, a funnel chest, spina bifida, bilateral saber deformity of the tibia and hallux valgus.

The anemia resulting from sickle cell disease is hemolytic in nature. The pathogenesis has been obscure. In 1940 one of us (J. B.)¹ advanced the theory that the anemia is caused by the deterioration of masses of deformed red blood corpuscles which are impacted in the smaller blood vessels of various organs, chiefly in the spleen and liver. Stagnation and conglutination of the red cells, such as are seen in cases of sickle cell anemia, must eventually lead to disintegration of the corpuscles without regard to whether or not an actual thrombosis did develop. The disintegration of the conglutinated erythrocytes sets free hemoglobin which is transformed into the hematogenous pigment found in various organs and into bilirubin found in increased amounts in the blood serum.

We have been interested in seeking for some other pathologic state associated with circulatory stasis in small blood vessels in order to study the effect of such a stasis with regard to the clinical symptomatology and particularly with regard to the occurrence of a hemolytic anemia. Such an analogous morbid state was found in a rare disease described first by Moschcowitz,¹⁶ later by Baehr, Klemperer and Schifrin,¹⁶ and Gitlow and Goldmark¹⁷ and more recently by Altschule.¹⁸ According to the last-named author, it is a "rare type of acute thrombocytopenic purpura: widespread formation of platelet thrombi in capillaries." The cause of those platelet thrombi is unknown, but the large masses of thrombocytes involved with the formation of thrombi probably account for the peripheral thrombocytopenia and subsequent purpura.¹⁶ No attempt is made here to discuss the nature of this disease. We agree with Altschule, however, that "attempts to relate this syndrome to acute disseminated lupus erythematosus because of the purpura and the finding of vascular lesions are not valid." What matters here is the occurrence of generalized capillary and arteriolar thromboses, whatever their cause and pathogenesis may be.

13. Kobak, A. J.; Stein, P. J., and Daro, A. F.: Sickle Cell Anemia in Pregnancy, *Am. J. Obst. & Gynec.* **41**:811 (May) 1941.

14. Footnotes 1, 4 and 6.

15. Moschcowitz, E.: An Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries, *Arch. Int. Med.* **36**:89 (July) 1925.

16. Baehr, G.; Klemperer, P., and Schifrin, A.: An Acute Febrile Anemia and Thrombocytopenic Purpura with Diffuse Platelet Thromboses of Capillaries and Arterioles, *Tr. A. Am. Physicians* **51**:43, 1936.

17. Gitlow, S., and Goldmark, C.: Generalized Capillary and Arteriolar Thrombosis, *Ann. Int. Med.* **13**:1046 (Dec.) 1939.

18. Altschule, M. D.: A Rare Type of Acute Thrombocytopenic Purpura: Widespread Formation of Platelet Thrombi in Capillaries, *New England J. Med.* **227**:477 (Sept. 24) 1942.

If our conception of sickle cell disease is correct, then similar consequences of a widespread thrombosis are to be expected as they are observed in sickle cell disease. In fact, anemia is such a consequence of both diseases. Moschcowitz¹⁵ as well as Baehr, Klemperer and Schiffrin¹⁶ entitled their report "an acute febrile anemia." This anemia must also be hemolytic in nature because it is frequently associated with icterus and because the bone marrow was found to be normal or showed a slight tendency to hyperplasia. The fragility of the red cells, when they were tested, was also found to be normal. Polymorphonuclear leukocytosis occurs both in sickle cell disease and in this peculiar malady. It is particularly remarkable that generalized aches and pains, especially about the joints, that diffuse abdominal pain with vomiting and that cerebral symptoms have been observed in this disease. Brain symptoms, such as confusion, mumbling speech or facial weakness, may disappear completely after a few minutes.¹⁸ At autopsy, increase in the number of lymphocytes in the periportal areas in the liver and slight hyalinization of the media of the splenic arteries have been found. Anemic infarcts of the spleen and abundant amounts of iron pigment in the pulp have also been reported.

It need not be emphasized that this rare malady and sickle cell disease have nothing in common as far as their causation and pathogenesis are concerned. Both diseases, however, are characterized by circulatory stasis caused by widespread obstruction of small blood vessels, though the mechanism of this obstruction may be different in each. We are fully aware of the inability of ruling out the possibility that the hemolytic anemia in the cases of thrombocytopenic purpura may be due to the same unknown factor which causes the formation of platelet thrombi and may, therefore, be of different nature than the hemolytic anemia in sickle cell disease. Yet the far reaching similarities between both diseases enumerated seem to be more than suggestive that the circulatory stasis occurring in both may account for most of the clinical symptoms and signs and particularly for the hemolytic anemia. Nature frequently supplies facts that are just as valuable for the basis of conclusions as animal experiments carried out in laboratories. One has only to recognize such facts, note them by proper clinical observation and make intelligent interpretation.

SUMMARY

The 7 cases reported demonstrate various consequences of the constitutional sickle cell trait.

Anemia is not an obligatory sign of sickle cell disease.

Serious consequences may result from the circulatory stasis in the small blood vessels rather than from the anemia.

Anemia in sickle cell disease is explained as a consequence of the deterioration of the conglutinated distorted red blood cells that cause the circulatory stasis.

Persons with the sickle cell trait are potential candidates for sickle cell disease with or without anemia. They are frequently representatives of a status degenerativus and are biologic liabilities.

Many cases of sickle cell disease are not diagnosed correctly because the sickling phenomenon is not looked for.

All Negro patients in both medical and surgical services should be tested routinely for sicklemia.

This demand is particularly made with regard to the armed forces.

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CUTIS GRAFTS; APPLICATION OF THE DERMATOME-FLAP METHOD

ITS USE IN A CASE OF RECURRENT INCISIONAL HERNIA

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AND

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DETROIT

REVIEW OF THE LITERATURE

The use of cutis grafts in the place of free fascial transplants has received scant attention from American writers. Until 1942, when Cannaday made his first report,¹ the use of cutis grafts in this country was limited almost exclusively to the field of plastic surgery, in which it is applied in the reconstruction of tissue defects.

In 1913, Loewe² reported the first cases in which cutis material was used as a buried graft, including repair of inguinal and umbilical hernia and tendon repair. Six cases were reported, and these are included as a matter of historical interest.

CASE 1.—Injury of extensor pollicis longus tendon. It was impossible to approximate the severed ends of the tendon, so cutis material was used to bridge the defect. The functional result was not satisfactory.

CASE 2.—Inguinal hernia. A piece of the cutis 7 cm. by 3 cm. was sutured over Hesselbach's triangle and a piece 5 cm. by 2.5 cm. over the canal. A postoperative hematoma was aspirated, and the wound healed with no recurrence of the hernia.

CASE 3.—Umbilical hernia and midline laparotomy incision. The wounds were connected and the entire wound covered with a cutis graft 10 cm. by 4 cm.

CASE 4.—Double inguinal hernia. The canals on both sides were covered with cutis 5 cm. by 2.5 cm.

CASE 5.—Bladder hernia, inguinal. A piece of cutis 6 cm. by 3 cm. was sutured over the transversalis fascia; then the muscles were united to Poupart's ligament over the graft.

CASE 6.—Castration through inguinal approach. A weak inguinal canal was covered with cutis graft. Infection and scrotal abscess occurred postoperatively.

Loewe, in describing the technic for removal of the graft, stated that the skin was removed in the manner of any full thickness graft. The epidermis was then abraded away by scraping, as one would scrape a carrot. This tissue was then sutured over the defect under tension.

Again, in 1929, Loewe³ reviewed his use of cutis grafts in nearly a hundred patients, adding numerous new procedures, such as using cutis material as sutures in gastroenterostomy, the replacement of dura, nerve suturing, arthroplasty and gastropexy. He observed that these grafts heal in place and that epidermoid elements tend to degenerate. Most of his results were favorable.

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1. Cannaday, J. E.: The Use of the Cutis Graft in the Repair of Certain Types of Incisional Herniae and Other Conditions, *Ann. Surg.* **115**:775-781 (May) 1942.

2. Loewe, O.: Ueber Hautimplantation an Stelle der freien Faszienplastik, München. med. Wchnschr. **60**:1320-1321, 1913.

3. Loewe, O.: Ueber Haut-Tiefenplastik, München. med. Wchnschr. **76**:2125-2128 (Dec. 20) 1929.

Following the work of Loewe, Rehn⁴ (1914) first reported his experimental use of cutis material. His experiments consisted mainly in twisting strips of cutis material and using it as an insert graft after performing a tenotomy on the achilles tendon of dogs. Rehn varied Loewe's technic in removing the epidermis with a razor, thus effecting less trauma to the tissue to be used. He observed that under the influence of continual tension, a gradual degeneration of epithelial characteristics occurred, and the tissue assumed the appearance and function of normal tendon in about ten weeks.

Uihlein,⁵ in 1939, reviewed the work of Rehn, and presented a series of 104 cases done in the University Clinic at Freiburg since 1928. He stated that Rehn concluded that cutis is the most suitable material for repairing defects because it most adequately fills the requirements for tissue regeneration.

Cannaday¹ (1942), the first American writer to report the use of cutis grafts in hernial repair in this country, reviewed the literature and presented 14 cases in which he had used cutis material in place of fascial transplants or free fascial grafts in the repair of hernia. In 1943, Cannaday⁶ made a later report, adding to his original cases and bringing his total to 37 in which cutis grafts had been used, 27 of which were hernial repairs.

Before going any further, it would no doubt be advisable to qualify and define the term cutis graft. Uihlein⁵ stated: "This word was coined by those who suggested the use of this type of skin graft because, though it is derived from the skin, it is not a bona fide skin graft. It does not contain the cutaneous and subcutaneous structures of skin, but it is devoid of its epidermal covering when it is transplanted."

The use of the cutis graft has no doubt been limited because of the mistaken conception that it might lead to the formation of epidermoid cysts. Rehn⁷ and his co-workers (1924) demonstrated conclusively from animal experimentation that the cutis graft takes on the characteristics and function of the tissue surrounding it and that in its use in repair of hernia, it forms a strong, fibrous tissue. Loewe² had the opportunity to make a microscopic study of pieces of cutis grafts implanted during a previous operation, and observed that the tissue showed retrogression of sweat and sebaceous glands, without cyst formation. Uihlein⁵ was able to make a microscopic study of tissue removed from a healed cutis transplant area of 2 patients on whom cutis operations had been done four years previously. He found that the preparations presented normal connective tissue with its fibrous and fatty components containing their own blood and nerve supply, and that the tissues demonstrated an abundant vascularity. He was able to find no epidermal remnant of the original cutis graft and no dermoid cysts could be identified. Peer and Paddock⁸ (1937) stored pieces of dermis beneath the skin in a series of plastic reconstruction operations and recovered them later, after varying lengths of time. Microscopic sections of the tissue demonstrated a gradual process of degeneration of normal skin structures, the sweat glands and the hair follicles being the first to disappear, so that

4. Rehn, E.: Das kutane und subkutane Bindegewebe als plastisches Material, München. med. Wchnschr. **61**:118-121, 1914.

5. Uihlein, A., Jr.: Use of the Cutis Graft in Plastic Operations, Arch. Surg. **38**:118-130 (Jan.) 1939.

6. Cannaday, J. E.: Some of the Uses of Cutis Graft in Surgery, Am. J. Surg. **59**:409-419 (Feb.) 1943.

7. Rehn, E., in Lexer, E.: Die freien Transplantationen, Stuttgart. Ferdinand Enke, 1924, pt. 2, p. 503; cited by Uihlein.⁵

8. Peer, L. A., and Paddock, R.: Histologic Studies on the Fate of Deeply Implanted Dermal Grafts, Arch. Surg. **34**:268-290 (Feb.) 1937.

finally a strong, fibrous tissue remained. Our own experimental work with dogs has borne out the results of Rehn⁴ and Peer and Paddock,⁸ showing the gradual transformation to fibrous tissue and demonstrating that cutis takes on the functions and characteristics of the tissue which it replaces.

In reviewing the literature on the subject, one of us (S. A. S.) was impressed with the difficulty of repair and suturing of the area from which the cutis graft was

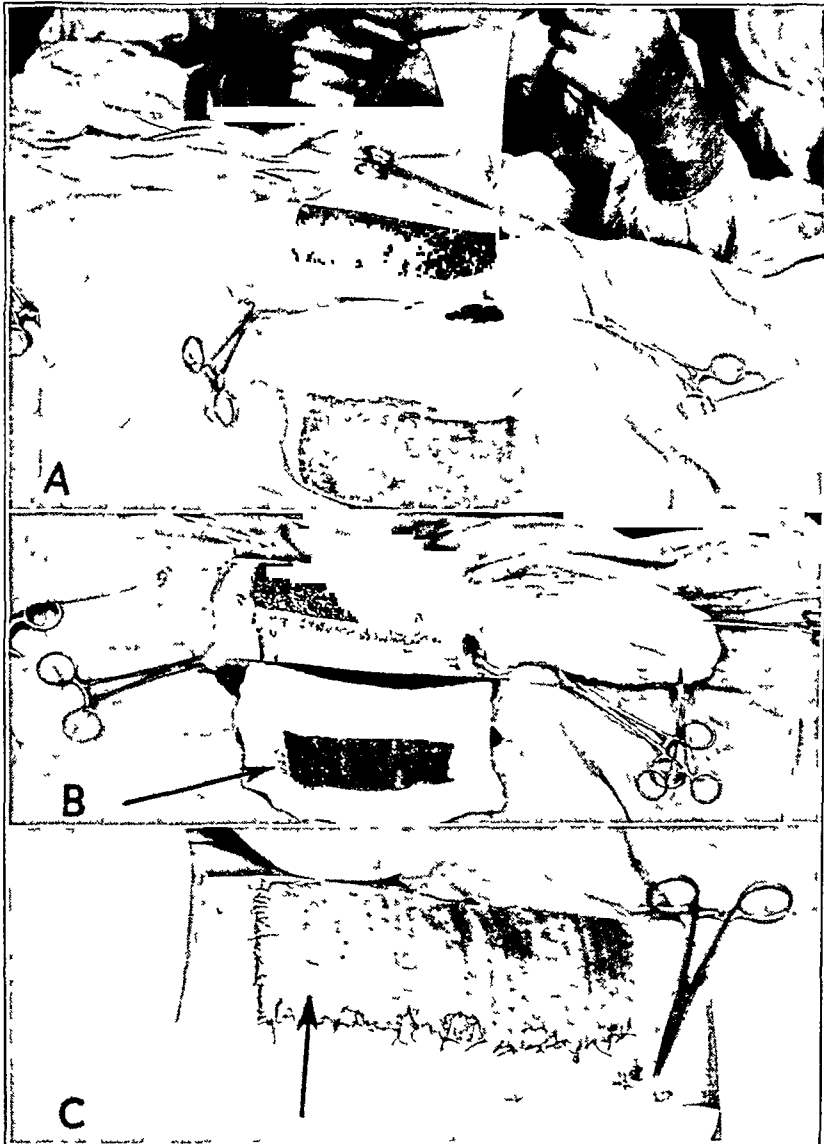


Fig. 1—*A*, dermatome graft still attached at lower end after removal from right thigh. The blotted pattern of the donor area is shown at the bottom of the figure below the wound. *B*, removal of cutis. The dermatome flap has been reflected down on the moist gauze to the right and is held at the edges with hemostats. The cutis (indicated by arrow) has been removed from the bed of the graft and it is seen that the removed cutis is not quite as large as the graft bed. The removed and slightly shrunken cutis is resting on a piece of gauze below the wound. *C*, restored dermatome flap. The flap has now been sutured back in place with fine silk on all but its attached edge. The arrow denotes the edge of the removed cutis showing through the translucent skin graft.

excised. In his review of Rehn's work, Uihlein⁹ gave no indication as to the method of care of the cutaneous wound of the excision area. Cannaday⁹ also omitted a description of the repair of the cutaneous defect. As we had had recent experience with the dermatome-flap method of closing a relaxing incision, this technic seemed directly applicable in the closure of the defect in the skin left by the excision of the cutis graft. Thinking that the idea was original, we applied this method to the case which is presented in this paper, only to find that it is almost identically described in Maingot's¹⁰ *Post-Graduate Surgery* as being done by Rehn in Freiburg. Maingot's description is as follows:



Fig. 2.—*A*, hernial repair by Mayo technic. The cutis has not yet been applied. *B*, application of cutis. The piece of cutis has now been applied over the fascial repair and has been sutured with interrupted silk under moderate tension, both across the bed of the graft and around its edges.

A dermal transplant should be cut to the size of the defect to be covered. After the defect has been defined, a template may be cut in sterile jaconet. With a skin graft razor, of which Humby's pattern is the most reliable when large areas are concerned, a Thiersch graft, some-

9. Cannaday,^{1,6} Peer, L. A.: Types of Buried Grafts Used to Repair Deep Depressions in the Skull, *J. A. M. A.* **115**:357-360 (Aug. 3) 1940.

10. Maingot, R.: *Post-Graduate Surgery*, New York, D. Appleton-Century Company, Inc., 1937, pp. 3608-3610.

what longer than the dermal patch required, is cut from the outer side of the thigh, but hinged at one end. The jaconet template is applied to the denuded derma, and the required patch cut round and dissected off with some underlying fat. The Thiersch flap is laid back on the raw surface which remains, retained in position with three or four marginal stitches, and pressed down with a firm dressing.

Maingot also states:

While fascial suture will solve most of the problems that can possibly confront the surgeon in the way of repair, it must be remembered that fascia lata, or any aponeurosis transmitting

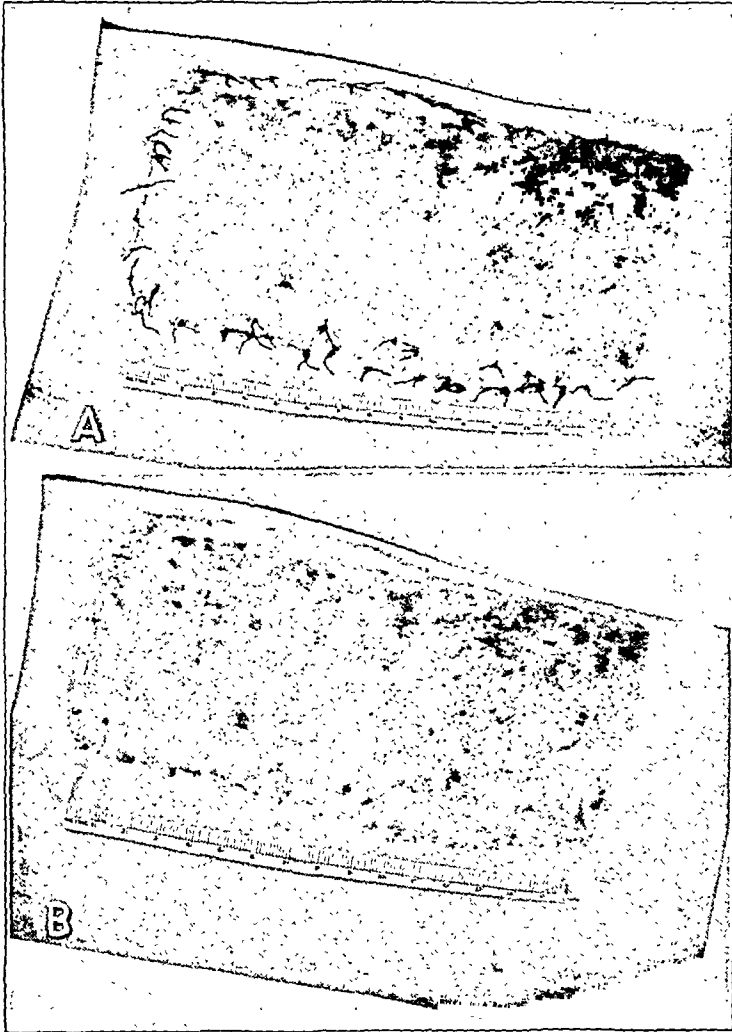


Fig. 3.—*A*, healed donor area on seventh day after operation. *B*, same after removal of sutures. The graft is essentially a 100 per cent take.

the pull of a muscle, is strong only in the direction of that pull. Its longitudinal fibers are held together by very few transverse ones, and large patches, even when securely anchored all round, are quite unfitted to take a strain applied equally to all their margins. The body, however, possesses in the derma a connective tissue sheet of almost unlimited size and strength, a felt-work of tough interlacing fibers equally strong in all directions. We use derma to sole our boots, cover our saddles, drive our machinery; and to paraphrase, one of the oldest sayings runs "there's nothing like derma."

REPORT OF A CASE

L. E., a white man, aged 40 years, was first admitted to the Henry Ford Hospital on April 4, 1940, at which time a diagnosis of nonfunctioning gallbladder was made and operation was advised. Operation on April 9, through a Kocher incision by another surgeon, revealed empyema of the gallbladder. The gallbladder was removed, and the wound was drained. The patient recovered and was discharged on April 26. He returned on Sept. 2, 1942, complaining of a dragging pain in the area of the operative wound, and a diagnosis of ventral incisional hernia was made. Operation was advised, and on September 9 the patient was operated on, at which time multiple peritoneal bulges were evident along the line of the entire incision. A Mayo repair was attempted, but because of lack of good tissue, only a single layer approximation was accomplished. The patient made an uneventful recovery and was discharged on September 24. He was without symptoms referable to the hernia until Feb. 18, 1943, at which time he stated that he again had pain at the incisional site. Examination revealed a recurrent incisional hernia, and operation was done on May 13.

Operation.—In view of the possible depth of penetration of contaminating organisms in the glandular structures of the skin, it is necessary to cleanse the area from which the graft is to be taken with meticulous care. The anterior or lateral surface of the thigh is an ideal



Fig. 4.—Abdominal wound five weeks after operation.

donor site in conditions such as hernias of the abdominal wall. Before the operation, the right thigh was shaved and scrubbed with tincture of green soap for ten minutes. The thigh was then washed with alcohol and ether, and a dry sterile dressing was applied before the patient was taken to the operating room. The entire procedure was done under nitrous oxide anesthesia in order that photographs might be taken.

The dressings were removed from the right thigh, and the area was again washed with alcohol and ether. The size of the desired cutis graft was determined and was marked out on the drum of the Padgett-Hood dermatome by first applying the glue to the entire surface of the drum and then carefully wiping away the glue from the edges with a dry sponge, leaving the glue present over the desired area. The blade of the dermatome was set at five and one-half notches or 0.11 mm. and the split thickness epidermal portion was removed, leaving the lower end to form a flap measuring 25.2 sq. in. (162.59 sq. cm.), as determined with a planimeter (Keuffel and Esser) from a gauze pattern taken at the time of operation and traced on paper, as illustrated in figure 1A and as described by Harkins¹¹ (1943). The cutis graft was then marked out on the remaining dermis with the scalpel and the tissue, measuring 22.1 sq. in. (142.58 sq. cm.) as determined with the planimeter as just described, was removed by sharp dissection, to but not including the subcutaneous fat, much in the manner of removing a full thickness skin graft, as illustrated in figure 1B. This

11. Harkins, H. N. A New Type of Relaxing Incision The Dermatome-Flap Method. *Am. J. Surg.* 59:79-82 (Jan) 1943.

maneuver is greatly facilitated if, after the leading edge is dissected free, that edge is clamped to a roll of gauze bandage. Continued dissection of the graft is done easily, the gauze roll being used as a firm drum on which clean dissection is made possible.

After the graft was removed and placed between layers of gauze soaked in saline solution, the split thickness flap was dropped back on the donor area, in the manner described by one of us (H. N. H.¹¹), and was sutured into place, fine black silk being used as illustrated in figure 1 *C*. The grafted area was then covered with petrolatum gauze and an elastic pressure dressing was accomplished by the use of an elastic adhesive bandage.

The field was then shifted to the hernial site, where the scar was excised and dissection was carried down to the sac. After incision of the sac, the fascial edges were identified and were approximated as well as possible, double, heavy silk sutures being used, with an attempt at the overlapping technic of Mayo, illustrated in figure 2 *A*. A small amount of sulfanilamide crystals (not more than 1 or 2 Gm.) was sprinkled on both sides of the graft tissue, and the graft was then sutured in place over the defect with interrupted silk sutures under as much tension as possible, it being made sure that the underlying anterior rectus sheath was devoid of fat and that hemostasis was complete, as illustrated in figure 2 *B*. Additional sutures were further placed around the edges, producing even tension throughout the surface of the graft. Sulfanilamide crystals were then lightly sprinkled over the graft to combat any possible organisms which might be present deep in the dermic structures, and the subcutaneous tissues were approximated with fine silk, dead space being obliterated by inclusion of the surface of the graft in each suture. A small cigaret drain was brought out through the lateral pole of the wound, and the skin was closed with interrupted fine silk sutures.

Postoperative Course.—The drain was removed on the second postoperative day. On this day dyspnea and cyanosis suddenly developed, with a rise in temperature. A diagnosis of pulmonary atelectasis, at the base of the left lung, was made. A large amount of mucus was aspirated from the left bronchus, with much relief to the patient. He was placed in an oxygen tent, which was removed on the fifth day, when the temperature receded to normal. The rest of the postoperative course was uneventful. The dressings on the abdomen and the graft area were changed on the seventh day (May 20, 1943), revealing the split thickness flap graft area healing primarily as illustrated in figure 3 *A*. Sutures were removed from the graft area and abdominal wound on the seventh day, and at no time was there any evidence of a fluid collection in the abdominal wound. Although Cannaday⁶ stated that he allows his patients to be out of bed the day after operation, we kept our patient in bed until the fifteenth day, and he was discharged from the hospital on May 31. Subsequent follow-up revealed complete healing of the abdominal wound with excellent support, as illustrated in figure 3 *B*, the photograph being taken June 15. The dermatome flap graft over the cutis excision area has remained perfectly healed, as shown in figure 4.

SUMMARY

A review of the literature on cutis grafts reveals that their use in the United States has been almost entirely limited to the field of plastic surgery.

Cutis material is easily obtainable and is universally applicable in the repair of hernial defects.

The dermatome-flap method of closure of the cutis donor area is presented as previous reports have omitted description of any satisfactory method of closure.

We are carrying on further experimental work on cutis grafts at the present time.

PENETRATING WOUNDS OF THE HEART

A ROUTINE OF MANAGEMENT BASED ON A FIVE YEAR PERIOD OF
PERSONAL OBSERVATION AND ON FIVE PERSONAL CASES

HARRY NELSON, M.D.

NEW ORLEANS

Although wounds of the heart have been diagnosed almost since prehistoric times, their surgical treatment is less than fifty years old, the first two operations, both unsuccessful, having been performed in 1895. Some twenty years earlier the great Billroth,¹ himself a pioneer in many fields of surgery, had written of paracentesis of the pericardium that it approached "very closely to that kind of intervention which some surgeons would term a prostitution of the surgical art and others madness," and had further stated that any surgeon who attempted to suture the living human heart would "lose the respect of his colleagues." In 1896 Stephen Paget² said flatly that surgery of the heart had "probably reached the limits set by nature to all surgery; no new method and no new discovery can overcome the natural difficulties that attend a wound of the heart." It is ironic that in that same year Rehn³ performed the first successful suture of a cardiac wound.

I avail myself of this opportunity to stress the pioneer work of Dr. R. Matas in the field of surgical cardiology, because in this, as in so many other fields related to the progress of surgery, especially at the Charity Hospital, he has led the way not only by his example as a teacher but by the originality, value and volume of his publications which are indicated in the bibliography.^{3a}

Examination of the records reveals that the first deliberate thoracotomy at Charity Hospital for a stab wound of the heart was performed on April 7, 1897 by Dr. Matas, who stated in reporting the case: "The chest was opened, the heart exposed and held in the hand in order to search for the wound which involved the wall of the Left Ventricle, but did not penetrate and required no suture." This

From the Independent Surgical Service of Charity Hospital of Louisiana at New Orleans.

1. Billroth, cited by Elkin.⁷

2. Paget, S.: *The Surgery of the Chest*, London, J. Wright & Co., 1896.

3. Rehn, cited by Schiebel, H. M.: *Stab Wound of the Pulmonary Artery with Suture and Recovery: Report of a Case with a Brief Review of Traumatic Cardiac Surgery*, Arch. Surg. **45**:957-963 (Dec.) 1942.

3a. Matas, R.: *Surgical Treatment of Perforating and Bleeding Wounds of the Chest*, J. A. M. A. **32**:687-692 (April 1) 1899; *Surgery of the Chest*, Tr. Louisiana State M. Soc., May 1898; *Recent Advances in the Technic of Thoracotomy and Pericardiotomy for Wounds of the Heart*, Tr. South. Surg. & Gynec. A. **20**:175-188, 1908; *South. M. J.* **1**:75-81, 1908; *Surgery of the Vascular System: Surgery of the Heart and Pericardium*, in Keen, W. W.: *Surgery: Its Principles and Practice*, Philadelphia, W. B. Saunders Company, 1909, vol. 5, chap. 70, pp. 1-350; *Military Surgery of the Vascular System: Surgery of the Heart*, in Keen, W. W.: *Surgery: Its Principles and Practice*, Philadelphia, W. B. Saunders Company, 1921, supp. vol. 7, pp. 713-819; *Routes of Access to the Heart: Lesions Gathered from the Experiences of the World War*, M. Rec. **99**:595-599 and 629, 1921; *Personal Experiences in Vascular Surgery*, Ann. Surg. **112**:802-839 (Nov.) 1940; Third Presentation on Nov. 14, 1940 of the Matas Award in Vascular Surgery to Dr. Daniel C. Elkin for Outstanding Contributions in Cardiorrhaphy. Proceedings and addresses with special reference to Dr. Matas' discussion of the experiences in suture of cardiac wounds at the Charity Hospital of New Orleans. Report of Committee of Award, New Orleans, Tulane University, 1940, pp. 7-15

event well antedated the first recorded American cardiorrhaphies, 2 of which were performed by Nietert, of St. Louis, in 1901, the first with operative mortality and the second with complete success.

Until very recent years, however, cardiorrhaphy remained in the nature of a surgical *tour de force*, and reports of its performance were chiefly the records of single cases. The literature on the subject is still confused, and even in the most careful reviews it is difficult to determine how much collected series overlap. Furthermore, it is clear that the rate of success has always seemed larger than it actually is, because statistics seldom take into account the number of patients with wounds of the heart who die without diagnosis, who die without treatment or who die after unreported operations. There is no doubt, for example, that among the 1,612 stab wounds of the chest treated at the Charity Hospital of Louisiana at New Orleans over the ten year period ending Dec. 31, 1940 were some undiagnosed wounds of the heart.

In 1934 Ramsdell⁴ collected 428 surgical cases reported prior to Jan. 1, 1932, in which the mortality ranged from 24 to 75 per cent and averaged 50 per cent. In the same year von Remetei⁵ mentioned a series of 535 surgical cases with a mortality of 55 per cent. Recently several relatively large single series have been reported, in which the distribution of the incidence and mortality furnishes interesting contrasts. Bigger,⁶ who reported 25 operations with 9 deaths in 1940, pointed out that the first cardiorrhaphy in the Medical College of Virginia Hospital was not performed until 1930, but that 25 such operations were performed in the next nine years. Elkin,⁷ who reported 38 operations with 16 deaths from Emory University Hospital in 1941, stated that the number of treated wounds of the heart had increased steadily each year since 1930. McGuire and McGrath⁸ reported in the same year that the mortality from wounds of the heart at the Cincinnati General Hospital prior to 1937, when conservative therapy or aspiration (if tamponade was present) was the practice, was 82 per cent. After that time, when operation became the rule in all diagnosed cases, the mortality fell to 23 per cent (3 of 13 operations). Griswold and Maguire,⁹ writing in 1942, stated that prior to 1933 only 3 operations on the heart, only 1 of which was successful, had been performed at the Louisville City Hospital. Since that date 22 operations had been done, with 6 deaths, and only 1 death had occurred in the last 13 cases.

Analysis of cardiac wounds at the Charity Hospital of Louisiana at New Orleans shows a precisely similar trend. Matas previously tabulated all of the recorded cardiorrhaphies at Charity Hospital from the first (and successful) one, done in January 1913 by Dr. Joseph Danna, to one done in October 1940 by Dr. Mims Gage. There were 17 operations by eight surgeons, with 11 deaths, or a mortality of 65 per cent.

4. Ramsdell, E. C.: Stab Wounds of the Heart, *Ann. Surg.* **99**: 141-151 (Jan.) 1934.

5. von Remetei, F. F.: Ueber die Stichverletzungen des Herzens nebst zwei Fällen, *Zentralbl. f. Chir.* **61**: 1723-1726 (July 21) 1934.

6. Bigger, I. A.: The Diagnosis and Treatment of Heart Wounds, with a Summary of Twenty-Five Cases, *South. M. J.* **33**: 6-11 (Jan.) 1940.

7. Elkin, D. C.: The Diagnosis and Treatment of Cardiac Trauma, *Ann. Surg.* **114**: 169-185 (Aug.) 1941.

8. McGuire, J., and McGrath, E. J.: Penetrating and Lacerating Wounds of the Heart, *Tr. A. Am. Physicians* **56**: 194-200, 1941.

9. Griswold, R. A., and Maguire, C. H.: Penetrating Wounds of the Heart and Pericardium, *Surg., Gynec. & Obst.* **74**: 406-418 (Feb., no. 2 A) 1942.

I am now able to report a series from February 1940 to October 1943 of 11 cardiorrhaphies by six surgeons, with 1 death, a mortality of 9 per cent. Of this group I personally performed 5 and am responsible for the single death.

The surgeons who have performed the operations reported in the entire series, from 1913 to 1943, are (chronologically) Drs. J. Danna, G. Graffagnino, E. Irwin, M. O. Miller, J. Landry, F. Planche, M. Gage, A. Ochsner, H. Kahle, R. Hays, H. Nelson, D. Williams, J. DiLeo and G. Martin.

The striking increase in the number of cardiorrhaphies performed at Charity Hospital in recent years is not due to any increase in the incidence of cardiac wounds but rather to a change in the surgical point of view concerning them. More correct diagnoses are being made because wounds of the heart are being suspected in more cases of thoracic injury. More operations are being performed on patients suspected of having wounds of the heart because the resident staff, which for obvious reasons handles the majority of such cases, is better informed concerning them, because of the rapidly accumulating store of information in the periodical literature, if for no other reason.

This information, incidentally, is chiefly contained in the periodical literature. Textbook discussions of the subject are for the most part thoroughly unsatisfactory. They usually consist of a discussion of cardiac tamponade, with therapeutic advice confined to the statement that only prompt operation can save the patient. It is to be hoped that new texts and new editions of standard texts will include the valuable material now available in the recent surgical journals.

DIAGNOSTIC CONSIDERATIONS

The diagnosis of cardiac wounds has been so excellently discussed by so many writers that not a great deal need be said about it here. It is not particularly difficult when the classic picture is present, including: (1) a period of freedom from symptoms, followed by rapid collapse and unconsciousness; (2) weak heart sounds associated with a weak pulse; (3) lowered arterial pressure, and (4) elevated venous pressure. Not a great deal of emphasis, however, has been placed on the fact that this picture is not present in all cases, particularly in cases in which automatic decompression occurs and tamponade is absent because the wound in the pericardium communicates with the pleural cavity or with the external surface of the body. Blegen¹⁰ is one of the few writers to call attention to this phenomenon.

Many lives will be lost unless there is constant emphasis on the fact that a wound of the heart is a possibility in any instance of penetrating thoracic injury, particularly when there is evidence of (1) cardiac tamponade, (2) progressive tension pneumothorax, (3) marked or progressive hemothorax and (4) shock other than that resulting purely from traumatic stimuli. These criteria, alone or in combination, furnish absolute indications for exploration of the chest. This opinion is based on a five year period of clinical observation in the Charity Hospital of Louisiana at New Orleans, which, with its large Negro population, offers a wide experience with wounds of violence.

A consideration of the phenomena of shock and of their background furnishes further support for prompt exploration in all cases in which diagnosis is not immediately evident. Watchful waiting, as Moon¹¹ has cautioned, is likely to be

10. Blegen, H. M.: Wounds of the Heart: A Review of Seventeen Cases with Four Operations, *Journal-Lancet* 63: 1-7 (Jan.) 1943.

11. Moon, V. H.: Shock: Its Dynamics, Occurrence and Management, ed. 2, Philadelphia, Lea & Febiger, 1942.

disastrous with any condition in which shock may develop. A patient in shock presents a vicious cycle initiated by hemorrhage, going on to hypotension and culminating in anoxia or hypoxia, which would seem the preferred term as more accurately expressing a decrease below physiologic limits in the supply of oxygen available for the tissues. Hypoxia is also aggravated by decreased vital capacity incidental to fluid in the pleural cavity or to tension pneumothorax. Both experimental and clinical observations show that not a great deal of hemorrhage is necessary to set in motion this vicious cycle and that the loss of small quantities of blood, which would be insignificant in a normal subject, may be lethal to a patient suffering from shock from any cause.

It is also important to emphasize again the now well known fact that a patient suffering from incipient shock or already in a state of shock may present no immediate clinical evidence of his condition. Blalock,¹² Moon¹¹ and others have repeatedly pointed out that the vital signs are an unreliable guide to the state of the circulation in incipient shock and that a progressive decline in the arterial pressure, with its accompanying evidences of circulatory deficiency, should be interpreted not as evidence of impending shock but rather as evidence of departed opportunities for treatment.

My associates and I have repeatedly corroborated these observations at the Charity Hospital of Louisiana at New Orleans. Patients with thoracic wounds, in whom the extent of the injury was not immediately apparent, have been kept under constant careful observation and yet either have died while under observation or have deteriorated so rapidly as to preclude surgical intervention. It has also been observed that patients who were brought out of primary shock but who again entered a state of shock while conservative therapy was practiced were unlikely to recover, regardless of the adequacy of later treatment. This clinical observation substantiates Blalock's¹² experimental demonstration that prolonged hypotension due to repeated bleedings is attended with a mortality of 100 per cent, even though the quantity of blood provided by transfusion actually exceeds the amount of blood withdrawn.

The final argument for exploratory thoracotomy in cases of suspected cardiac damage is that the exploration is attended with a minimal mortality. During five years of observation in the accident and emergency surgical service at Charity Hospital, I have never seen a death attributable to simple opening of the chest for exploratory purposes.

THE ILLOGIC OF CONSERVATIVE THERAPY FOR CARDIAC TRAUMA

The most valid reason for resorting to prompt operation for cardiac wounds is that a long trial of conservative therapy over many years has shown that in spite of occasional brilliant results the mortality of this method is very high. It was 90 per cent in the 452 cases of penetrating wounds of the heart collected by Fischer¹³ in 1868. That some patients recover without operation is no argument for nonsurgical therapy, in view of the impossibility of determining in which cases that happy outcome will be achieved.

Incidentally, the fact that a patient is apparently moribund should not deter one from operating. Bullock's¹⁴ suggestion is sound, that even a moribund sub-

12. Blalock, A.: Shock: Further Studies with Particular Reference to the Effects of Hemorrhage, *Arch. Surg.* **29**: 847-857 (Nov.) 1934.

13. Fischer, G., cited by Blegen.¹⁰

14. Bullock, W. O.: The Ultimate Phase of Life as It Relates to Wounds of the Heart, *Ann. Surg.* **103**: 696-697 (May) 1936.

ject should be submitted to what Blegen¹⁰ has called "a quick thoracic autopsy," which would be his only hope of salvation. In Bullock's own case the patient was thought to be dead before the pericardium was opened, but operation was proceeded with (in order, Bullock stated frankly, that he might gain experience in operating on the heart) and survival followed.

Another argument against conservative therapy is that it may be followed by undesirable consequences. Rehn,³ who performed the first successful cardiorrhaphy on record, advocated suture of the wound if only because an unsutured wound might leave a weak heart. Elkin⁷ and Strieder,¹⁵ writing along the same lines, have both pointed out the possibility of the development of aneurysm of the coronary vessels or of the myocardium. Another objection to conservative therapy is the possible development of pericardial adhesions. A case of this sort was observed at Charity Hospital. The patient presented symptoms of heart failure, which had first appeared after conservative treatment of a wound of the heart at another institution. A diagnosis of pericardial adhesions was made and cardiolysis was attempted, but the adhesions were too dense and widespread to be released and death followed.

Aspiration of the pericardial cavity, whether as a method of diagnosis or of treatment, is mentioned only to be condemned. It furnishes no information not usually available by other methods, its permanent therapeutic value is always debatable, and it may do considerable harm. In 1 case in which it was practiced at Charity Hospital the patient died instantly. Autopsy showed that the needle had penetrated one of the coronary vessels.

ROUTINE OF MANAGEMENT

The management of suspected or proved wounds of the heart at Charity Hospital is based on the concept that cardiac hemorrhage does not differ from any other variety of internal hemorrhage and that the best opportunity for survival in any case of internal bleeding is offered by prompt control of the bleeding, preferably at the source.

A patient with a penetrating thoracic wound in which absolute indications for exploration of the chest are not present is submitted to a period of observation and diagnostic testing, which never exceeds thirty minutes. During this period all preparations for operation are carried out. He is placed in the Trendelenburg position, and morphine and scopolamine are given in doses appropriate to his weight and age. Oxygen inhalations (by mask or tent) are also begun at once. If prompt and progressive improvement ensues under these measures, it is assumed that the state of shock has resulted from traumatic stimuli rather than from persistent hemorrhage or pulmonary compression or a combination of these conditions. A patient who does not improve promptly is given the benefit of an exploratory thoracotomy.

The wound is examined under aseptic precautions as soon as sedatives have been administered. A wound made with a knife or other large instrument is usually immediately perceptible, but careful examination may be necessary to identify a wound made with an ice pick or a similar small weapon. A sucking wound is closed with a pressure dressing, and treatment for tension pneumothorax is begun. Mediastinal emphysema is treated by incision above the manubrium sterni and insertion of a rubber catheter into the mediastinum. Unless these two

15. Strieder, J. W.: Stab Wound of the Heart Report of a Case Treated Conservatively. *J. Thoracic Surg.* 8: 576-577 (June) 1939.

complications demand immediate treatment, a simple sterile pressure dressing is placed over the wound while further diagnostic measures are proceeded with.

The point of maximum impulse is indicated on the wall of the chest and is observed frequently, to detect a possible shift of the mediastinum. The pulse, respiratory rate and blood pressure are checked at frequent intervals, as is the venous pressure. The venous pressure is usually elevated in patients with cardiac wounds, but a low pressure is not incompatible with this type of injury and would be expected in shocked patients or in patients in whom automatic decompression of the pericardium is possible. Diagnosis in this type of case may be extremely difficult, but in cases in which the venous pressure is greatly elevated a high degree of tamponade may be assumed and operation should be proceeded with at once.

Repeated determinations of the blood concentration are useful in detecting incipient shock. Roentgen examination is sometimes helpful in demonstrating the extent of the initial hemothorax and pneumothorax but is unreliable in demonstrating the existence of hemopericardium.⁷ Bigger⁸ has emphasized the value of fluoroscopy in demonstrating the obliteration of pericardial pulsations and the immobilization of the heart shadow, but our policy of performing an exploratory operation in all doubtful cases makes this diagnostic aid unnecessary. Electrocardiographic study is not employed as a preoperative measure.

Typing and cross matching of blood are carried out in all cases, and transfusion, preferably with whole blood, is begun as soon as a supply of blood or plasma is available in all cases in which exploration is to be done. The replacement of blood is so important that autotransfusion was employed in 1 of my early personal cases. The establishment of a blood and plasma bank at Charity Hospital made this measure unnecessary in later cases. The blood is introduced through an intravenous cannula, since experience has shown that its free and uninterrupted flow may mean the difference between life and death. The rate of flow, however, is always slow until the cardiac wound has been closed.

External heat is the only routine antishock measure which is not employed. It has been found that reduction of the environmental temperature by thermostatic control (the emergency and operating rooms at Charity Hospital being air-conditioned) gives better results than the use of heat.¹⁶ Unless the stomach is known to be empty it is emptied by suction before anesthesia is begun.

ANESTHESIA

My preference is for cyclopropane or ethylene-ether anesthesia, which should be given by a skilled anesthetist and by the endotracheal route.^{16a} This form of anesthesia maintains a constant and adequate airway, provides adequate relaxation and yet at the same time furnishes a maximum concentration of oxygen, a consideration of paramount importance for a patient suffering from actual or potential hypoxia. McGuire and McGrath⁸ attributed a high percentage of pulmonary complications

16. Cooling in Shock, editorial, J. A. M. A. **121**: 432-433 (Feb. 6) 1943.

16a. This method of anesthesia was initiated by Dr. Matas with his modification of the Fell-O'Dwyer tube which he introduced at Charity Hospital in 1899. His apparatus allowed the introduction of chloroform or ether vapor with positive pressure. (Matas, R.: On the Management of Acute Traumatic Pneumothorax, *Ann. Surg.* **29**:409-434, 1899; Intralaryngeal Insufflation for the Relief of Acute Surgical Pneumothorax: Its History and Methods with a Description of the Latest Devices for This Purpose, *Tr. South. Surg. & Gynec. A.* **12**:52-84, 1900; Artificial Respiration by Direct Intralaryngeal Intubation with Modified O'Dwyer Tube and New Graduated Air-Pump [Matas-Smyth Pump] in Its Application to Medical and Surgical Practice, *Tr. Am. S. A.* **19**:392-411, 1901; *Am. Med.* **3**:97-103, 1902.)

in their series of cases to the use of general anesthesia, but this has not been my experience. Local infiltration has been advised by several writers, but I am opposed to it for at least three reasons: 1. It is time consuming. 2. It does not permit the endotracheal airway possible in inhalation anesthesia. 3. It furnishes no control over the patient's movements. Patients with cardiac wounds are frequently under the influence of alcohol, and their clouded mental state is often aggravated by the cerebral manifestations of hypoxia.¹⁷ As a result, their uncontrolled movements under local analgesia may do a great deal of harm.

SURGICAL TECHNIC

The chest is opened by a transverse incision with a vertical extension along the parasternal line, the location of the incision depending on the location of the injury. A single rib is resected subperiosteally, and such additional space as is necessary is provided by the simple division of one or more adjacent ribs. The extrapleural approach is undesirable for several reasons. It is more time consuming than the transpleural approach. Exposure is less satisfactory. Pleuropericardial drainage is not obtained. No matter how careful the technic, the pleural cavity is often opened accidentally. Bigger⁶ has called attention to this accident, and it has been observed in several cases at Charity Hospital. Finally, and most important, the extrapleural approach serves no useful purpose, since the pleural space must always be explored for possible damage to the lung and to adjacent vessels.

If possible, the traumatic wound is excised when the surgical wound is made. If this is not possible, it is carefully isolated until the close of the operative procedure. Then it is debrided, irrigated and insufflated with sulfathiazole powder before it is sutured. Infection of the wound is a serious possibility in cardiac trauma. I have followed this plan in all 5 of my cases and have never witnessed it personally.

If careful exploration of the pericardium reveals no evidence of laceration or of contained blood, it is not opened and the possible damage caused by the penetrating wound is sought for elsewhere. Otherwise the pericardium is incised vertically along its lateral surface. All preparations have previously been made to place at least one suture instantly if the cardiac wound presents at the opening, before forcible cardiac contraction returns with the relief of tamponade. Occasionally it is possible to place all the sutures before forcible contraction returns. Aspiration of the contained pericardial blood and clots is then carried out. This technic greatly simplifies the insertion of sutures in the heart and is usually possible if the surgeon is alert to grasp the opportunity.

If the wound does not immediately present, 1 per cent solution of procaine hydrochloride is injected into the vagus nerve before any further manipulation is attempted. The rationale of this step is the observation by anesthetists that traction on the heart or bronchus is likely to be followed by bradycardia or cardiac asystole, the risks of which need no elaboration. The plan was suggested to me by the studies of Weiss and Ferris¹⁸ on the hyperactive carotid sinus reflex, and I feel that occasional deaths from cardiac asystole will be prevented by its use.

The use of a traction suture, in my opinion, is always undesirable. The heart can be rotated manually quite as satisfactorily and with less trauma. Furthermore,

17. Batten, C. T., and Courville, C. B. Mental Disturbances Following Nitrous Oxide Anesthesia, *Anesthesiology* 1: 261-273 (Nov.) 1940.

18. Weiss, S., and Ferris, E. B., Jr. Adams-Stokes Syndrome with Transient Complete Heart Block of Vagovagal Reflex Origin. Mechanism and Treatment, *Arch. Int. Med.* 54: 931-951 (Dec.) 1934.

a traction suture occasionally tears through, as happened in 1 case observed at Charity Hospital.

The heart wound is closed with interrupted cotton intestinal sutures. Sutures of this material, as Meade and Ochsner¹⁹ have shown, produce a minimum of reaction in the tissues. If hemorrhage complicates the closure or makes it impossible, gentle digital pressure directly over the defect is usually effective. The finger, as Beck²⁰ warns, should not be placed in the wound, from which it would be forced out with each beat of the heart, but over it. If this plan is not effective the Sauerbruch²¹ maneuver should be employed: The vena cava is compressed by passing the left hand between it and the transverse sinus. Compression should be very brief. The coronary vessels should be visualized, so that sutures will not be placed through them or include them.

After the presenting wound has been closed, the entire heart is inspected for possible further damage. In 4 of the cases observed at Charity Hospital the wounds were multiple, and in 1 instance the second wound was not found until the patient had died on the table after closure of what was thought to be a single wound.

The pericardium is now cleared of accumulated blood and clots, irrigated with warm isotonic solution of sodium chloride and closed with a row of interrupted cotton sutures. A small opening is left at the upper angle for drainage. I prefer drainage in this area to the more commonly employed drainage opening at the inferior angle of the wound. The lower opening drains off not only excess pericardial fluid but also normal amounts, which should be left in situ to prevent friction and subsequent inflammation. No other form of drainage is employed unless suppuration is definitely anticipated.

After the pericardium has been closed, the lung, mediastinum, diaphragm and mammary and intercostal vessels are inspected for possible damage, which is corrected according to the indications. The pleural cavity is then irrigated with warm isotonic solution of sodium chloride, both to check for a possible leak of air and to reduce by dilution possible bacterial contamination. After the solution has been suctioned out, sulfathiazole (5 Gm.) in suspension is placed in the cavity and the wound is closed about an oxygen catheter with interrupted cotton sutures. Separate closure of the pleural layer is not necessary. The catheter is removed just before the last suture is tied, and the excess of oxygen is removed by suction. The replacement of the intrapleural atmosphere by oxygen was first practiced in Overholt's²² clinic by Betts and Cotton, to whom it was suggested by Welkin and Herman's work on rapid reexpansion of the lung after the institution of pneumothorax in tuberculosis. Pulmonary reexpansion should never be accomplished by manual compression of the anesthetic bag, because of risk of trauma to the alveoli.

POSTOPERATIVE THERAPY

Some patients who would otherwise have survived operation on the heart have probably lost their lives because of poorly directed or actually inadequate postoperative therapy, and too much importance cannot be attached to this phase of treatment. It has several objects: (1) the prevention or correction of hypotension,

19. Meade, W. H., and Ochsner, A.: Spool Cotton as a Suture Material, *J. A. M. A.* **113**:2230-2231 (Dec. 16) 1939.

20. Beck, C. S.: Further Observations on Stab Wounds of the Heart, *Ann. Surg.* **115**: 698-704 (April) 1942.

21. Sauerbruch, cited by Elkin.⁷

22. Overholt, R. H.: Personal communication to the author.

(2) the prevention or correction of hypoxia, (3) the prevention of cardiac tamponade, (4) the prevention of cardiac failure and (5) the achievement of maximum repair of the tissues.

The closure of the cardiac wound, the transfusion of an adequate amount of blood and the administration of oxygen are usually followed by correction of hypotension. The patient is kept on the operating table until this object is achieved. Transfer to the ward before the arterial pressure has been stabilized at an approximately normal level is unwise, since the pressure may drop still further in transit. If the pressure does not rise within a reasonable time, a fatal outcome is likely, since hypoxia and irreversible injury to the central nervous system are consequences of prolonged hypotension.

On his arrival in the ward, the patient is placed in a tilted bed, with the head elevated. This position makes respiration easier and is a prophylaxis against peripheral vascular thrombosis. Morphine is used in amounts barely sufficient to control pain, because of its tendency to depress the respiratory centers and thus aggravate hypoxia. Oxygen is given continuously by mask or tent. Additional transfusions are given if the hemoglobin or red blood cell count is low, and plasma is used if the concentration of the blood is abnormally high or if the serum protein content is low. Otherwise a proper fluid balance is maintained by carefully regulated intravenous infusions of dextrose and isotonic solution of sodium chloride. Chemotherapy is employed only on definite indications. Vitamin concentrates, especially ascorbic acid, are administered in large doses. Bigger,⁶ who lost a patient in whom a clot completely filled the right ventricular cavity, has proposed the use of heparin after operation if the wound has penetrated any of the chambers of the heart or has divided important coronary vessels, and the rationale of the suggestion is clear. Practical considerations, however, make the general employment of this method unlikely.

The patient is not permitted out of bed for at least three to four weeks, and it is impressed on him that his resumption of his usual activities must be carefully graded.

The most important postoperative complications are: atelectasis, pulmonary compression and pneumonitis, all of which are related to hypoxia; pericarditis, which causes tamponade, and myocardial infarction.

Prophylaxis against atelectasis includes moving the patient from his back to the involved side at intervals, until he is able to move himself, and encouragement of coughing and deep breathing exercises. The onset is heralded by hyperpyrexia and by the usual symptoms of hypoxia, namely, hyperpnea, elevation of the pulse rate, elevation of the arterial pressure and sometimes psychotic manifestations. It should be emphasized that diffuse bilateral atelectasis may occur with few or no demonstrable physical findings. The statement that the absence of cyanosis implies adequate oxygenation is by no means true. Lundsgaard and Van Slyke²³ demonstrated many years ago that for physical reasons cyanosis cannot appear in patients who have less than 5 Gm. of hemoglobin per hundred cubic centimeters of blood, because of the dilution of their blood. In other words, the paradoxical situation exists that the patient most likely to have fatal hypoxia, because of his lack of hemoglobin, is least likely to manifest cyanosis, while the patient whose condition is much less critical is more likely to present it, because his supply of hemoglobin is adequate.

23. Lundsgaard, C., and Van Slyke, D. D.: Cyanosis, *Medicine* 2: 1-76 (Feb.) 1923.

If atelectasis should occur, postural drainage and aspiration with a bronchial catheter should be carried out without delay. If this aspiration is unsuccessful, bronchoscopic aspiration should be carried out with equal promptness.

Pulmonary compression which develops soon after operation is usually the result of either tension pneumothorax or hemothorax. Tension pneumothorax is treated by the immediate insertion of an intrapleural cannula connected with a water trap. Minor degrees of hemothorax need only careful observation. Progressive hemothorax is treated by aspiration, supplemented by transfusion as necessary. Neither tension pneumothorax nor hemothorax is likely to occur if exploration and operative technic have been adequate.

Delayed pulmonary compression is usually the result of pleural effusion, the development of which can be foreseen in routine serial roentgenograms. The fluid is removed only if it is present in sufficient amounts to cause symptoms or if there is undue delay in pulmonary reexpansion. An occasional and seldom remembered cause of pulmonary compression is elevation of the diaphragm as the result of gaseous distention of the intestinal tract. In such circumstances dyspnea may be alarming, and relief is dramatic when gastroduodenal suction, the rectal tube and enemas are used.

The management of pneumonitis and of myocardial infarction does not differ from their management under other circumstances. The taking of serial electrocardiograms is a wise precaution after operation, particularly if the coronary vessels have been implicated in the wound. In 1 such case at Charity Hospital serial electrocardiograms showed typical coronary occlusion. Improvement was progressive, but a symptomless myocardial infarct was still present when the patient disappeared from observation about four months after operation.

ANALYSIS OF CASES

From Jan. 1, 1906 to the date of writing 27 cardiorrhaphies have been performed by 13 surgeons at the Charity Hospital of Louisiana at New Orleans. I performed 5 operations, with 1 death, and Dr. Mims Gage²⁴ performed 4, with 1 death. The death of my patient was entirely preventable and should not have occurred: The patient presented a good risk, and operation was undertaken promptly and carried out without special difficulty. Because of a confusion of priorities, however, the hospital supply of oxygen masks and tents had been exhausted, and oxygen in high concentration could not be supplied. Autopsy revealed left ventricular dilatation, a small pleural effusion and moderate bilateral pulmonary edema. None of these was sufficient in itself or in combination with other pathologic changes to explain the death; all of them, however, pointed to hypoxia as the basic cause of the fatality.

All 27 patients were Negroes, and all but 1 were men. The majority were under 30 years of age, but 2, 50 and 53 years of age respectively, are among the oldest recorded in the literature. Dr. D. B. Williams,²⁵ who has already reported the case, operated on the 50 year old subject, and I operated on the 53 year old man. Curiously, the ice pick, on which Elkin, whose experience is chiefly with Negroes, has frequently laid stress, was used in only 1 instance in the Charity Hospital series. All the other injuries were caused by knives of various sizes. All

24. While the proof was being corrected, Lieutenant Colonel Mims Gage accomplished another successful cardiorrhaphy while functioning as a medical officer in the Fourth Service Command.

25. Williams, D. B.: Successful Suture of Stab Wound of Heart, *New Orleans M. & S. J.* 95: 470-472 (April) 1943.

the implements had been removed, either by the assailants or by the victims themselves, before hospitalization, and the diagnostic aid furnished by the coincident movement of the weapon and the heart was thus not present in any of these cases.

In the reports on 2 patients operated on early in this series no statement is made as to the location of the wound. In the remaining 24 cases the wound involved the apex in 1, the anterior surface in 1, the left atrium in 3, the right atrium in 5, the left ventricle in 9 and the right ventricle in 10. Elkin⁷ also found the highest incidence (14 of 38 cases) in the right ventricle and attributed it to the fact that this ventricle occupies the greater part of the anterior portion of the heart.

In 4 cases the wounds were multiple. In the first case there were two wounds of the left ventricle. In the second case the wound involved the right ventricle and the right atrium. In the third case it involved the right atrium and both ventricles. In the fourth case it involved the right ventricle and the right atrium. The last 2 patients, who were operated on by Dr. Mims Gage and Dr. J. L. DiLeo respectively, both survived. The longest wound, which I personally sutured, measured approximately 2.75 cm. and required six stitches.

The postoperative complications in the last 11 cases in this series included pleural effusion in 8 cases, in 1 of which it was bilateral, wound infection in 2 cases, and myocardial infarct and hemothorax in 1 case each. Tension pneumothorax, postoperative hemorrhage, postoperative tamponade, empyema and pulmonary complications were conspicuously lacking.

Associated pathologic states included laceration of the internal mammary vessels in 2 cases and of the coronary vessels in 1, a sucking thoracic wound in 1, and periapical pulmonary adhesions in 2. A sucking thoracic wound, if not promptly closed, is likely to bring on hypoxia rapidly, since it causes bilateral pulmonary compression. Periapical adhesions, which must be divided before the lung can be brought down and the pericardium exposed, prolong the operative procedure and increase the technical difficulties.

One patient I operated on had a preexistent pneumonitis. He had had bilateral bronchopneumonia and was left unattended while members of his family were working in the barroom over which they lived. While they were absent he slipped out of bed, left the house by a back door and went to another barroom, where he was stabbed in the heart. Fortunately, the pulmonary condition was readily controlled by chemotherapy.

The reduction in the mortality of cardiac wounds at Charity Hospital in the last three years can be attributed to a number of causes. One of the most important is the institution of a strict regimen of management, which means that when the patient reaches the hospital no time is lost in placing him on the operating table. The lapsed time between admission and operation in 1 of these cases was only fifteen minutes. The regimen of postoperative therapy is planned as carefully as the preoperative regimen, and a continuing endeavor has been made to develop an atraumatic technic, the steps of which have been described. Skilful anesthesia and the immediate availability of blood and plasma are other important reasons for the lowered mortality. Chemotherapy was used in all but 1 of the last 11 cases, but only on definite indications. The value of the sulfonamide drugs is granted, but it is felt that their role in the lessening of the mortality of cardiac wounds has been small. The basic cause for the reduction of the mortality is, as already indicated, the adoption of an attitude of suspicion, so that exploration is carried out in every instance of penetrating thoracic wound in which it cannot be said positively that a cardiac wound does not exist.

SUMMARY AND CONCLUSIONS

In recent years the number of operations for wounds of the heart has increased and the mortality has decreased. The 11 cardiorrhaphies performed in the last three years at the Charity Hospital of Louisiana at New Orleans, 5 of which I performed, reflect both these trends.

A detailed outline of preoperative management, anesthetic methods, surgical technic and postoperative therapy is presented.

Conservative therapy of cardiac wounds has given poor results, and there is no valid reason why such a wound should not be handled precisely as any other wound in which hemorrhage is a factor, that is, by control of the bleeding at the source.

The recent reduction in the mortality of cardiorrhaphy can be attributed to several causes, including promptness of operation, adherence to a detailed regimen of management throughout the case, and skilled anesthesia. The most important reason for the reduction, however, is the policy of performing an exploratory operation in all cases of penetrating thoracic wounds in which it cannot be determined positively that the wound has not reached the heart.

Dr. John Adriani, director of anesthesia at the Charity Hospital of Louisiana at New Orleans, gave invaluable suggestions regarding anesthesia and postoperative care. Miss Elizabeth McFetridge assisted in the preparation of the paper.

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A FLEXIBLE PLASTIC-LIQUID ADHESIVE

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The irritations, abrasions and dermatitis produced by adhesive plaster when used with wound dressings are too well known to require elaboration. In addition, there are many patients for whom adhesive plaster cannot be used at all, owing to allergies and extreme sensitiveness of the skin to the plaster. Two other disadvantages invariably connected with the use of adhesive plaster in surgical dressings are the varying degrees of discomfort to the patient and the necessity for removing adhesive debris with solvents that may further irritate the skin.

The foregoing objections led to a search for a substance which could be used in place of adhesive plaster and which would have the following characteristics: (1) adhesive qualities, (2) elasticity, (3) ease of application, (4) ease of removal without debris, (5) freedom from toxic and allergic effects, (6) ready availability, (7) low cost and (8) freedom from staining.

In order to achieve these effects, an experiment was conducted at Montefiore Hospital for Chronic Diseases in which adhesive plaster made from natural resins was replaced with a liquid adhesive made from synthetic resins.

Solutions of polyvinyl butyral resin in varying solvents and containing different plasticizers were applied to dressings and the skin in order to arrive at a combination of ingredients which would be most efficient for the purpose intended. The following formula was found to produce a liquid which possesses adequate adhesive qualities and elasticity, is capable of easy removal without leaving debris on the skin and is readily available and inexpensive:

Polyvinyl butyral resin ¹	20 Gm.
Alcohol (95 per cent).....	120 cc.
Ether	20 cc.
Castor oil	10 cc.

The polyvinyl butyral resin is placed in the mixture of alcohol and castor oil and allowed to dissolve without stirring or agitation (admixture of air must be prevented). When the polyvinyl butyral resin is completely dissolved, the ether is added. The resulting solution is a clear, colorless liquid of high viscosity.

If the liquid is used, for example, on a gauze dressing 8 inches (20 cm.) square and $\frac{1}{2}$ inch (1.3 cm.) thick, it should be applied along a border 1 inch (2.5 cm.) to 2 inches (5 cm.) wide with a wooden applicator or spatula and the wet surface of the dressing should be placed against the skin. Pressure with the hand should be used for about one minute on the border of the dressing. This will make for quicker and better adhesion.

In order to determine whether the adhesive solution was irritating or capable of producing toxic reactions, or inducing allergies, tests were conducted on 175 patients in the Pulmonary Division of Montefiore Hospital and in the Montefiore Country Sanatorium.

These tests were conducted in the Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases, New York, and Bedford Hills, N. Y.

1. The polyvinyl butyral resin used in this experiment was vinylite xyse—purchased by Montefiore Hospital from the Carbide and Carbon Chemical Corporation, New York.

Then tests were carried out in which that basic solution was used with different plasticizers. These tests proved that best results were obtained with the use of castor oil and an organic compound (flexol) as plasticizers.

GROUP I

One hundred and seventy-five male and female patients in the wards of the Pulmonary Division of Montefiore Hospital were used as subjects. Thirty of these patients were known to be sensitive to the customary adhesive plaster. To an area 2 inches (5 cm.) square on the inner side of one forearm of each of the 175 persons, an application of the liquid adhesive was made and allowed to dry. The dried membrane of liquid adhesive was left on the arm for at least twenty-four hours, after which time observations were made. In no case was there redness or any noticeable abnormality of the skin, and none of the patients complained of itching or other discomfort. In order to investigate the possibility of delayed reactions, observations were again made on all the patients a week later, and the results were the same.

GROUP II

Fifty-three male and female patients were the subjects. Nineteen of these had had adhesive plaster burns within the past two years. Of these, 4 patients had adhesive plaster burns on the chest and back at the time of this experiment.

The procedure in this experiment was as follows:

The polyvinyl butyral resin liquid adhesive was applied to a 2 inch (5 cm.) gauze pad of an average of six thicknesses, which was placed on the skin of the subject. Seventeen male subjects had the dressings applied to the back, and 36 male and female patients (21 male and 15 female), to the arm. The dressings were applied in the manner previously described and permitted to remain for twenty-four hours, after which time they were removed, observations were made and new dressings were applied on the other arm and on the other side of the back. These dressings were kept on for twenty-four hours. Observations were made and the process repeated again until a total of twenty-eight to thirty dressings had been applied to each patient.

Thus there were over fifteen hundred dressings applied to 53 patients. All observations were negative except in 3 cases.

CASE 1.—Dressings were applied to the arms of a man daily for seven days with no noticeable reaction. On the seventh day the patient took a bath and left the dressings on. The following day the dressings were removed, and the skin appeared to be red and inflamed. New dressings were applied to the other arm, kept on for twenty-four hours and removed. No redness or other reaction was observed; however, the area covered by the dressing appeared red and inflamed the following day. Another dressing was applied, and the patient was instructed to wet the dressing; several minutes after he had done so, itching began. The dressings were removed, and the area of skin was red and inflamed. Itching lasted several minutes, and redness disappeared in four days.

CASE 2.—After eight days of application of dressings to the back, it was found that there was a slight redness of the skin underneath the dressings. Dressings were repeated at twenty-four hour intervals, and the redness persisted. After the last dressing the redness disappeared within three days and there was no other abnormal cutaneous manifestation.

CASE 3.—After nine repeated dressings at twenty-four hour intervals, a slight redness was observed on the skin underneath the dressings. No other cutaneous abnormalities were observed. Dressings were repeated at twenty-four hour intervals for five more days. Redness persisted under the dressings, and the patient complained of a slight itch while dressings were on. The redness disappeared after three days. No other cutaneous manifestations were observed.

In these cases, after periods of seven, eight and nine days respectively, a slight redness appeared on the skin, accompanied by a minor irritation on the removal of the dressings. After three or four days the symptoms disappeared, and there were no other abnormal cutaneous manifestations.

COMMENT

In all cases the patients expressed the opinion that the polyvinyl butyral resin dressings were more comfortable than the adhesive plaster dressings they were used to, and in all cases dressings were easily removed without any debris remaining on the skin and without use of solvents.

Further experimentation is indicated for the use of solutions of polyvinyl butyral resin for the protection of the skin surrounding draining fistulas, and against the macerating and irritating effects of the exudates. Experimentation is also indicated to determine the advantage of the admixture of specific medicaments with the liquid adhesive used in this experiment.

Brief studies were made of solutions of polyvinyl butyral resin with ethyl cellulose and aluminum dust. These mixtures were applied to the skin surrounding draining fistulas and were found to afford greater protection against the maceration caused by the exudates than was possible by applications of ointments. The use of water-shedding agents, such as aluminum stearate and zinc stearate, aided in protecting the skin.

SUMMARY

A liquid adhesive has been produced which possesses sufficient elasticity and is capable of being applied with ease and removed without leaving any debris on the skin. The fact that 19 patients unable to tolerate the customary adhesive plaster were unaffected by this liquid adhesive, with the possible exception of 3 persons mentioned, gives evidence as to its usefulness as a substitute for adhesive plaster.

370 Cypress Avenue.

PROGRESS IN ORTHOPEDIC SURGERY FOR 1942

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE AMERICAN
ACADEMY OF ORTHOPAEDIC SURGEONS

XI. CONDITIONS INVOLVING THE SPINE AND THORAX EXCLUSIVE OF THOSE IN THE LOWER PART OF THE BACK

PREPARED BY JOHN R. COBB, M.D., NEW YORK

(Continued from page 515)

Haas³¹⁸ reports a case of spastic scoliosis with obliquity of the pelvis treated by surgical transference of muscle. The patient had considerable pelvic obliquity and a left lumbar scoliosis. The author points out that it is important to obtain a balancing of the muscle pull on both sides of the pelvis and the thoracic cage. He points out that scoliosis with pelvic obliquity due to spastic paralysis is an infrequent entity: "The correction of this deformity is difficult because of the complicated causative mechanical factors, the disorganization of normal muscle control, incoordination, and disturbance in equilibration. It is important that, in attempting a correction of this deformity, one does not further disrupt locomotion by increasing the imbalance or enhance the ability of accommodation for co-existing deformities."

The author considers the possible methods of correction in this type of case. He feels that spinal fusion would have to include the sacrum with the lumbosacral joint and all the lumbar vertebrae. "In view of the bad results obtained with this type of fusion in cases of poliomyelitis, it was thought to be particularly inadvisable in spastic paralysis. A constant strong unilateral pull may cause a return of the deformity with permanent fixation. A spastic patient with disturbance in equilibration may need the free movement of the spine and pelvis to maintain his balance."

[ED. NOTE.—It seems important to stress the point that a spastic patient with disturbance in equilibration may need the free movement of the spine and pelvis to maintain his balance. This is a definite argument against the use of spinal fusion in cases of spastic scoliosis. However, many orthopedic surgeons will not agree with the author regarding the bad results obtained with fusion in cases of poliomyelitis, and it should be pointed out that some surgeons have had excellent results. The results following fusion in cases of poliomyelitis depend considerably on such factors as the technic used and the type of correction.]

The author discusses the use of a strut graft from the ilium, which he considers inadvisable. He also discusses the release of the sacrospinalis, lateral abdominal, anterior abdominal and quadratus lumborum muscles, which would entail an extensive dissection, a difficult problem of balance of pull and the possibility of herniation and other bad sequelae. Neurectomies or other nerve-destroying operations on the involved muscles are not considered advisable. The author also mentions that fascial slings or checks from the ribs to the pelvis on the opposite side, such as have been used in poliomyelitis, may be successful. The opposing strong constant pull would tend to stretch the fascia unless a compensatory hypertrophy took place. There is also the difficulty of completely fixing one half of the pelvis.

The author points out that the greater pull of the spastic muscles on the right side over the normal pull of the muscles of the left side was considered to be

318. Haas, S. L.: Spastic Scoliosis and Obliquity of Pelvis, J. Bone & Joint Surg. **24**:774-780 (Oct.) 1942.

responsible for the scoliosis and the obliquity of the pelvis. If some of the pull of the anterior and posterior muscles could be transferred to the opposite side and the correct balance obtained, the deformity could be permanently corrected. As it could be actively corrected by the use of the Carl Jones splint, it was known that no permanent structural changes had taken place. If the method did not work, then some of the other methods could be utilized to supply any deficiency. The author then describes the two operations by which he transfers the pull of the external oblique and rectus abdominis muscles and also the pull of the latissimus dorsi and longissimus dorsi muscles, by use of fascial strips and transfer of muscle. He points out that it is possible that the same type of correction could be secured in early paralytic scoliosis before fixed contracture and structural changes had occurred in the vertebrae. "It would be necessary to know definitely which groups of muscles are involved before any muscle transference operation could be performed. Unfortunately it is not easy to determine this fact in many cases of scoliosis."

[ED. NOTE.—It should be stressed here that it is not easy to determine which group of muscles is involved in most cases of paralytic scoliosis. Also paralytic scoliosis frequently stops increasing and does not progress beyond the early stage, so that many unnecessary operations might be done. The author concludes that "transference of muscles in association with fusion operations may help to reduce the loss of correction and the tendency to recurrences following fusion operations for scoliosis of the spine." While marked muscular imbalance may cause a loss of some correction following spinal fusion in some cases of paralytic scoliosis, usually the loss of correction and the tendency to recurrence following fusion are due to the fact that the fusion is not adequately performed and completely solid, with an amount of bone adequate to hold the trunk mass. When the fusion is adequately done with a sufficiently large amount of bone, even pronounced muscle imbalance can often be overcome. The curvature frequently does not increase, and often most of the correction can be maintained.]

Wenger³¹⁹ in an article on rib resection in the treatment of scoliosis reviews the material previously reported in a paper by Wenger and Herman entitled "The Role of the Transverse Process in Thoracogenic Scoliosis" which was reviewed in "Progress in Orthopedic Surgery for 1941." He discusses the material presented in the previous article but draws other conclusions. The author states:

Analysis shows the following facts:

1. In the majority of the cases there was convexity of the spine toward the operative side.
2. The number and the length of the costal segments resected do not of themselves alter the resulting scoliosis.
3. In all cases in which there was marked convexity to the side on which operation had been performed either the transverse process was injured or the anterior costotransverse ligament was cut. In cases in which the transverse processes were left intact, slight curvature or none at all resulted.
4. In all the cases (3.5 per cent) in which the patients were children there was destruction of the transverse processes. This possibility explains the severe postoperative curvature.
5. Resecting a larger number of ribs does not necessarily increase the curvature. However, if a transverse process is injured or removed the curvature occurs.
6. Resection lateral to the angles of the ribs causes practically no deviation except in children.
7. There are no sharply angulated curves; that is, there are no wedged vertebrae. (All are C curves.)

319. Wenger, H. L.: Rib Resection in Treatment of Scoliosis, *Arch. Surg.* **44**:119-128 (Jan.) 1942.

8. As successive rib resections are carried out at lower levels, the apex of the curve descends.
9. Mediastinal displacement does not necessarily cause scoliosis.
10. There was no change in spinal curvature in 7 cases in which basal thoracoplasty was performed. Apparently basal thoracoplasty has little effect on the spine.
11. In cases in which successive ribs are removed and at one point a transverse process is resected, the apex of curve suddenly localizes at that point, and the curve increases.
12. Regeneration of ribs will prevent scoliosis.
13. In all cases the resulting curve averaged 18 degrees.

He concludes that scoliosis due to thoracoplasty results from trauma or removal of the transverse processes and that rib resection of itself has little, if any, influence in causing the condition. "On the basis of these findings transversectomy to correct primary scoliosis is now being done on the concave side of the spinal curvature."

[ED. NOTE.—It seems obvious that the cause of scoliosis following thoracoplasty is a disturbance of the bone-muscle mechanism supporting the spine. The ribs and their muscular attachments have a definite mechanical effect on the position of the spine. One of Wenger's patients had practically no scoliosis after resection of ribs on both sides. It is obvious that this would be true even if the transverse processes were resected. It is also obvious that the curvature is likely to be more deforming and more severe if there is great damage to the bone and muscle balance.

Therefore one would assume that resecting the transverse processes as well as the ribs would add to the instability. However, there are definite known cases of curvature, especially in children, in which the curvature developed following resection of ribs only. His series has only 9 children (3.5 per cent). This is a very small series, and he does not state how long they were followed nor how severe the curvatures were. He reports that the average resulting curve was 18 degrees. This is not a severe curve and does not require any treatment for the curvature itself, especially in adults. The serious part of the problem of scoliosis following thoracoplasty relates to the children whose later growth adds to the deforming factor. Most adults with scoliosis following thoracoplasty do not have severe curves and do not require much, if any, treatment for the curvature.

The author states that resection lateral to the angle of the ribs causes practically no deviation except in children. In many of the cases with only partial rib resection a small area is done, and in these patients such a severe scoliosis would not be expected to develop. Also, he does not explain why there is no deviation except in children. Why should scoliosis develop in the children if the transverse process were the only cause? It is obvious that if thoracoplasty on the left will cause a curvature of the spine convex to the left, such a procedure carried out in a child having a scoliosis convex to the right will result in a type of scoliosis likely to counteract the original tendency. However, thoracoplasty on the concave side of an idiopathic curve is an extremely drastic procedure. There is already beginning decreased vital capacity on the right side, which is the side of the convexity, and in performing a thoracoplasty on the left, one would have to remove sufficient ribs to decrease the vital capacity on the left as well as on the right. While mechanically this might seem worth a trial, clinically, considering the physiology of the patient, it seems entirely too radical a procedure.

Dr. Wenger states that he is doing a transversectomy on the concave side to attempt to correct scoliosis due to other causes, including idiopathic scoliosis. He does not note that in addition to resection of the transverse processes the patients

in this series also had resection of the ribs on the convex side. In other words, he has not established the fact that if the transverse processes alone are resected scoliosis will develop. He has merely shown that scoliosis develops after rib resection and resection of the transverse processes. It has yet to be shown whether resection of the transverse processes alone could cause scoliosis. It should also be pointed out that in probably 80 per cent or more of cases of so-called idiopathic scoliosis the deformity stops progressing when the curve is not severe enough to require any radical treatment. It would be necessary to do the resection of the transverse processes while the curve was very slight, in order to get any beneficial effect. It would therefore be easy to find a large series of cases in which the curve did not increase after resection of the transverse processes because in a large percentage it would not increase anyway. It would be difficult to prove that resection of the transverse processes actually was the cause of stopping the progressing scoliosis. The report of Dr. Wenger's cases in which he has done resection of the transverse processes for the treatment of scoliosis will be awaited with interest.]

Martin ³²⁰ reports 4 cases of atlaoxoid dislocation following cervical infection. He points out that while dislocation of the atlas on the axis is often traumatic, with fracture of the odontoid process and resultant damage to the cord, it may also occur as a sequel to cervical infections. This second cause brings the patient into the field of the otorhinolaryngologist, who deals with infections in this region and who must recognize the source of the dislocation. He feels that the best explanation of the pathologic changes which occur is that of Greig ³²¹:

. . . cervical infections, by producing hyperemia, cause vertebral decalcification of a greater or less degree. The ligaments are so strong that they cannot be avulsed without tearing off fragments of bone with them, but if the bone has undergone previous decalcification the ligaments yield readily.

Jones demonstrated this decalcification in some of his roentgen studies. He showed that it is peculiar to children at an age when the bones are imperfectly developed and not well calcified, that an inflammatory lesion anywhere in the upper cervical region may cause such decalcification; that the anterior arch of the atlas may show decalcification without destruction and, finally, that the onset of dislocation usually occurs about ten days after the infection begins.

Evidently Desfosses and Grisel believed that nasopharyngitis causes muscle spasm which produces the torticollis and vertebral subluxation, but Greig disagreed, asserting that the spasm of the prevertebral and occipitovertebral muscles splints the bones and is therefore a result, not a cause. These authorities gave the following sequence of events:

. . . (1) cervical infection with hyperemia, (2) vertebral decalcification and loosening of the ligamentous attachments, (3) slipping forward of one or both lateral articular facets of the atlas and locking as the facet slips forward and downward over the opposing facet of the axis, or (4) slipping backward of one articular facet of the atlas (if both lateral facets slip to any degree death may supervene since to permit this to happen the odontoid must have moved posteriorly and thus have crushed the cord). Berkheiser and Seidler presented 2 such cases in a series of 5, but they overlooked the fact that in any three-point suspension two points must always move, otherwise a fracture occurs.

The author points out that the patient holds his head rigidly, slightly in front of the normal plane tilted toward one shoulder with the face rotated toward the opposite shoulder. Tenderness over the lateral masses of the axis and atlas occurred

320. Martin, R. C.: Atlas-Axis Dislocation Following Cervical Infection, *J. A. M. A.* **118**:874-875 (March 14) 1942.

321. Greig, D. M.: *The Surgical Pathology of Bone*, London, Oliver & Boyd, 1931.

in all 4 of his cases. There is no spasm of the sternomastoid muscle such as occurs in "spastic" torticollis, the rigidity resulting from spasm of the deep cervical muscles. He says:

One may see an occasional case of torticollis preceding or following mastoidectomy and must be alert not to attribute it to an unconscious attempt on the part of the patient to relax an inflamed sternomastoid muscle on the diseased or operated side. Two of our patients whose dislocation was associated with mastoiditis, one occurring before operation and the other after operation, held the head tilted toward the sound side and the chin toward the diseased side. This position actually increased the strain on the inflamed muscle and caused me to consider the possibility that a cervical dislocation had in fact occurred.

It should be emphasized that care must be exercised in placing a patient for operation and in moving him postoperatively, particularly after severe or long-lasting cervical infections. In 1 case in our series (case 4) in which the dislocation was found after operation, the position on the table may have been partly responsible for the dislocation by stretching of the ligamentous attachments, though the dislocation did not occur until twenty-four hours after operation.

Two dislocations subsequent to tonsillectomy and 1 subsequent to local anesthesia have been reported. In another case there was gradual onset of dislocation for two weeks after an adenotonsillectomy. No neurologic signs or symptoms were present in any of the 4 cases; so there was no compression of the cord. The author accomplished reduction of the dislocation by accentuating the deformity in addition to traction, permitting unlocking of the lips of the lateral articular facets. Reposition of the vertebrae is secured by extension and by bringing the head to the midline while rotating the chin to its normal position. Fixation in plaster for a variable time allows healing and reattachment of the ligament. In 1 case a paper collar support was used after removal of the plaster. The results in all cases were good.

[ED. NOTE.—While atlas-axis dislocation following cervical infections have been previously reported, this article covers the problem well and again calls attention to the importance of not overlooking possible association of atlas-axis dislocations with cervical infections. Some later and prolonged orthopedic problems concerning the neck may be related to some of these conditions which have been neglected.]

Hess, Abelson and Bronstein³²² present a case of unreduced spontaneous atlanto-axial dislocation and suggest that this condition should be looked for in cases of unexplained kyphosis and scoliosis. They bring up the question whether unreduced atlantoaxial dislocation may play a role in the production of certain orthopedic conditions, such as wry neck, scoliosis and cervical arthritis. They report a case in which treatment was not given in which the dislocation persisted after a period of five years. They point out the importance of careful follow-up in the treatment of infectious diseases and of suppurative conditions about the head and neck in order to avoid this complication.

[ED. NOTE.—This condition has been previously reported, and in most cases simple traction with or without manipulation seems to be sufficient. Careful follow-up, including roentgenograms, is important.]

Weiler³²³ reports another case of congenital absence of the odontoid process of the second cervical vertebra or epistropheus, resulting in atlantoepistropheal dislocation. Fusion following reduction was successful. The patient has no symptoms after two years. Weiler briefly reviews the history of the subject as

322. Hess, J. H.; Abelson, S. M., and Bronstein, I. P.: Spontaneous Atlantoaxial Dislocations; Possible Relation to Deformity of Spine, *Am. J. Dis. Child.* **64**:51-54 (July) 1942.

323. Weiler, H. G.: Congenital Absence of Odontoid Process of Axis with Atlanto-Axial Dislocation, *J. Bone & Joint Surg.* **24**:161-165 (Jan.) 1942.

reported in the literature and points out that the dislocation may be reduced by continuous cervical traction or manipulation but that reduction of the dislocation appears insufficient unless fixation of the atlas is made to the axis to prevent recurrent slipping. For fusion the author used a short section of rib, split longitudinally and sutured to the first and the second cervical vertebra. In this case manipulation with the patient under cyclopropane anesthesia was necessary for reduction. The operation was done on the atlantoaxial area through a window in the back of the cast.

[ED. NOTE.—The congenital absence of the odontoid process of the axis with dislocation is relatively rare and is therefore worth mentioning in the review of the literature. It might also be pointed out that in most cases in which operation on the high cervical area is required, especially where there is a question of dislocation and mechanical instability with resultant danger of collapse during the operation, it is usually considered safer to perform the operation with traction on the skull rather than through a plaster. The operation has been done with plaster and with traction, and it has been done without either. Most surgeons feel that the operation is safer with the patient under skeletal traction with either tongs or wires in the skull.]

Jostes³²⁴ reports 9 cases in which laminagrams of the cervical vertebrae were an aid in diagnosis of occipitocervical lesions. He discusses the various conditions causing pain in the neck or occipital region with radiation toward one or both shoulders and the treatment for these cases, especially stressing the aid obtained by use of the laminagram.

[ED. NOTE.—Ordinary roentgenograms of the cervical vertebrae are frequently difficult to interpret, and the laminagram evidently should be used more extensively in these cases. Probably many patients whose pain is routinely relieved by such measures as traction on the head, immobilization and the wearing of a leather collar would fall into the class reported by Dr. Jostes if a laminagram had been taken and a more definitely localized diagnosis made.]

Craig, Walsh and Camp³²⁵ report on 3 patients with the roentgenographic picture of basilar invagination of the skull. In 2 of the cases associated anomalies of the upper cervical vertebrae also were present. In all 3 cases the clinical symptoms suggested involvement of the spinal cord in the upper cervical region and the brain stem, whereas the neurologic signs indicated a lesion of the cerebellum or its tracts. There was 1 case each of a lesion of the brain stem and a lesion of the spinal cord in the upper cervical region. Marked respiratory difficulty occurred in 1 case. In all 3 cases adhesions between the meninges and inferior poles of the cerebellar lobes and brain stem were noted at operation and freed. In 2 cases marked herniation of portions of the cerebellar lobes occurred. Relief from symptoms was striking in all cases.

The authors also point out that a characteristic roentgenographic picture of basilar invagination of the skull has been encountered among several patients who had neither clinical symptoms nor signs of involvement of the nervous system.

[ED. NOTE.—While previous cases of invagination of the skull have been reported in which improvement followed operation, this paper seems worth mentioning, for, as the authors point out, "Now that we are aware that 'platybasia' or

324. Jostes, F. A.: Neck Pain: Laminagraph as Aid to Diagnosis of Atlanto-Occipital Lesions, *J. A. M. A.* **118**:353-359 (Jan. 31) 1942.

325. Craig, W. M.; Walsh, M. N., and Camp, J. D.: Basilar Invagination of Skull—So-Called Platybasia: Report of Three Cases in Which Operation Was Done, *Surg., Gynec. & Obst.* **74**:751-754 (March) 1942.

more nearly accurately, basilar invagination of the skull, is a deformity of the occipital bone, which narrows the foramen magnum, and of the upper cervical vertebrae, which flattens the spinal canal and that removal of the bone which is compressing the underlying brain and spinal cord usually will be followed by relief of symptoms, the syndrome is receiving more recognition." Like many other obscure problems and syndromes, this condition will be frequently overlooked until it becomes better known by constant report of cases.]

Haynes³²⁶ reports a case of dural constricting ring with cervical protruded intervertebral disk. A severe arachnoid and dural reaction at the foramen magnum was interpreted as being secondary to a space-occupying lesion of the cervical portion of the spinal cord, in this case a protruded intervertebral disk.

In the absence of platybasia or other bony deformity, a dural and arachnoid constricting ring was found at the level of the foramen magnum, the reaction apparently starting at the level of the protruded intervertebral disk at the fifth cervical vertebra and extending cephalad, becoming very marked at the foramen.

It is suggested that, contrary to general opinion, the syringomyelic cavity below a dural constricting ring at the foramen magnum is not secondary to the malformation, but causes the dural and arachnoid reaction resulting in the malformation.

This report does not attempt to explain the syringomyelic cavity found in the cases of platybasia where the odontoid process has caused a dural reaction resulting in the same constricting ring.

This is an interesting report, and, as the author points out, the case tends to favor the belief of Hassin "that a long standing or advanced syringomyelic cavity or other space-occupying lesion of the cervical cord might cause meningeal changes." In this case the space-occupying lesion at the level of the fifth cervical vertebra was not a syringomyelic cyst but a protruded intervertebral disk. This lesion was accompanied by an arachnoid reaction, which surrounded it, extended upward and culminated in severe arachnoid proliferation, dural thickening and the formation of a dural constricting ring at the level of the foramen magnum. "Complete roentgenographic studies revealed no evidence of platybasia or upper cervical malformation and none was found at the time of operation."

[ED. NOTE.—This interesting case is well worth reporting and seems to contribute further to the knowledge of some of the rare and difficult conditions involving the upper cervical areas of the spine.]

Brown and Kuhns³²⁷ state:

The symptoms commonly found in the so-called scalenus syndrome and in cervical ribs may be caused by remote factors as well as local ones. The symptoms are frequently due to trauma, either from a definite strain or from the chronic strains which come in the use of the whole body, and especially of the chest and cervical spine, for a long period of time in faulty mechanics, combined with general relaxation and fatigue. In the authors' experience, the correction of the extension deformity of the cervical spine, combined with the correction of the faulty use of the body as a whole will bring relief of the neurological as well as of the vascular symptoms, in the majority of cases, without the necessity of operative procedures.

They also point out that

... the distribution of the symptoms will depend among other factors, upon the location of the habitual position of extreme extension of the cervical spine. If the apex of the curve is in the upper cervical region the distribution will be through the cervical nerve plexus; and, if in the lower cervical spine, the distribution will be through the brachial plexus.

326. Haynes, W. G.: Dural Constricting Ring with Cervical Protruded Intervertebral Disk: Report of Case, *New England J. Med.* **227**:825-827 (Nov. 26) 1942.

327. Brown, L. T., and Kuhns, J. G.: Extension Deformities of Cervical Spine, *J. Bone & Joint Surg.* **24**:329-340 (April) 1942.

~Aynesworth describes the scalenus and cervical-rib syndrome in the inclusive term cervical-brachial syndrome, and divides the cases into three groups: (1) those which exhibit neurological symptoms as their chief manifestation; (2) those which exhibit vascular symptoms as their major manifestation; and (3) those which exhibit a combination of vascular and neurological symptoms. This suggests the probability that there must be causes more widespread and remote than the usual explanation of local pressure from a thickened scalenus anterior or a cervical rib.

They describe the anatomy of the cervical vertebrae and give details of their treatment for extension deformities.

The object of treatment is to correct the extension deformities in the cervical and lumbar regions of the spine, and also the flexion deformity of the thoracic spine and the associated drooped chest. The correction of the extension deformity of the cervical spine is most easily accomplished by recumbency on the back on a firm mattress. To relieve the strain on the lumbar spine, a large pillow under the knees and a small pillow to fill the hollow in the low back is helpful. With this procedure muscle spasm subsides quickly in most instances. The authors have rarely found head-traction necessary. A felt collar, fitted low in front and high in back, to reduce the extension deformity, adds to the patient's comfort. The correction of the drooped chest and of the extension deformity of the lumbar spine is obtained gradually by exercises planned to correct the habitual faulty position of use. These are begun in recumbency and progress to the sitting and standing position, emphasis being laid upon good body mechanics rather than upon the exercises *per se*. When the ambulatory stage is reached, support for the spine and abdomen is usually necessary.

[ED. NOTE.—This is a good paper on symptoms referable to the cervical area, frequently seen in orthopedic surgery. The authors point out that occasionally operative treatment may be required and tend to confirm the view of many other orthopedic surgeons who have had success in the relief of scalenus anticus and cervical rib syndromes by conservative methods and without operation. It has been pointed out by others previously that probably 80 per cent or more of patients with the scalenus anticus or cervical rib syndrome can be relieved without operation, and it seems worth while to stress the conservative treatment. It is likely that many patients who have had operations for the scalenus anticus or cervical rib syndrome could have been relieved by conservative methods.]

Haggart and Toumey³²⁸ describe a method of spinal fusion which is a modification of the Hibbs procedure and in their hands has proved a most satisfactory technic. They describe the usual technic for exposure of the spine in the area to be fused and emphasize the importance of curetting the articular facets, stressing the point that it is important to obtain fusion.

[ED. NOTE.—There are a great many orthopedic surgeons who do not feel it is necessary to obtain fusion of the articular facets if a proper spinal fusion is done. Incidentally, the articular facets frequently will disappear after a period of years, even though they were not disturbed at the time of operation. The technic described by these authors is essentially a modification of the Hibbs technic with some variation in turning up and down the flaps or chips of bone from the laminae and in addition adding bone from the ilium. It should be noted that when the spinal fusion is performed through a hole in the plaster jacket, as is so frequently done, during the correction for scoliosis it is difficult or impossible to obtain bone from the ilium and therefore usually necessary to use tibial bone. It is also very likely that more bone and better osteoperiosteal strips can be obtained from the tibia. It should be noted that these authors still use the original procedure of removing the spinous processes entirely and making bone chips of them. Turning these chips up and down from the spinous processes without removing them is

328. Haggart, G. E., and Toumey, J. W.: *Spine Fusion: Effective Technique*, S. Clin. North America 22:873-881 (June) 1942.

preferred by many surgeons. The authors conclude that "meticulous attention to the details noted herein will result in a consistently firm fusion in the region operated on, as shown in the postoperative roentgenogram, which exhibits a large mass of bone that completely stabilizes the lumbosacral spine." This conclusion seems rather optimistic, since there is no method of spinal fusion which is 100 per cent successful in any one's hands. Incidentally, the reproductions of the roentgenograms are rather poor, and it is difficult to see the large mass of bone that they describe, at least in these reproductions.]

Crawford³²⁹ describes a method of extensive laminectomy with replacement of removed laminae. He says:

The easily approachable sharply localized protruded masses from ruptured intervertebral discs can often be adequately removed with minimal or no bone removal. This has the advantage of prompt convalescence and little or no weakening of the back.

In my experience there are some cases with good clinical history and findings of ruptured discs which at operation have shown neither a ruptured disc nor a thickened ligamentum flavum, but where the cause of nerve impingement has been one or more of the following anatomic structures: (1) The upper lip of the fifth lumbar facet, with a relaxed joint, associated with increased lumbosacral lordosis; (2) Hypertrophic arthritis resulting in a flaring out of the borders of the vertebral bodies, thus simulating a prominent intervertebral disc; (3) A structurally small intervertebral foramen due to bony changes or to increased tissue, including dilated lumbar veins, surrounding the nerves in the foramina.

Clinically these cases are similar to those due to ruptured discs, but are less likely to have clear-cut traumatic histories, usually have a more prolonged and intermittent course and although they may have improved with conservative therapy, have had repeated recurrences of pain and finally have become incapacitated. They may have bilateral signs or symptoms which may involve either or both of the fourth and fifth lumbar nerves.

To adequately expose these nerves on both sides by the usual method of laminectomy with rongeurs may leave a structurally weak back, as the facets may have to be removed.

In attempting to meet this latter problem, lately we have been removing in one piece with chisel and mallet, the entire dorsal arch composed of a spine, lamina, and attached facets. [ED. NOTE.—This procedure gives an excellent exposure of both nerves throughout their entire course through the foramina.] Sometimes we have had to chisel off the overhanging edge of the facet to free up an adherent involved nerve. At times enlarged veins accompanying the nerve through the foramina, appear to be an important etiologic factor.

After the nerves have thus been adequately decompressed and the removed bone fragment trimmed up so it cannot itself later cause nerve impingement and the cartilage of the facets has been scraped off to insure bony ankylosis, the piece is then returned to its bed and sutured in place with silver or stainless steel wire between the adjacent spines and facets. The patient is kept on a Bradford frame for a few days and then has a back brace fitted to be worn until the graft is safely grown in place.

The author states that this operation had been done on 7 patients during the ten months preceding the writing of his article, and thus far had proved to be satisfactory. It had given excellent exposure for thorough decompression without the weak backs which almost certainly would have resulted from the use of the old method. Also, the patients had been able to return to active work sooner than they would have with tibial bone grafts.

[ED. NOTE.—As the author points out, this is too small a group of cases to serve as a reliable guide, and more time should pass to see whether any unfavorable after-effects might develop. He does not advocate its use when the lesion is certainly unilateral and when it can be adequately relieved with a hemilaminectomy. It should be mentioned that the removal of this portion of the spine produces in effect a spondylolysis or prespondylolisthesis and creates the same mechanical situation found in prespondylolisthesis, in which the fifth lumbar body may slide

329. Crawford, A. S.: Method of Extensive Laminectomy with Replacement of Removed Laminae, *Surgery* 12:482-485 (Sept.) 1942.

forward on the sacrum. This extensive removal of bone might possibly add further complications by causing a spondylolisthesis, and the only thing to prevent this is a fusion between the denuded articular facets and the osteotomized pedicles when the large fragment is replaced. Also, following this procedure it is questionable whether there is sufficient assurance of fusion to warrant letting the patient up any sooner than one would after any operation for spinal fusion. The incidence of pseudarthrosis following lumbosacral fusions is high, and after this procedure the same problems of bone healing would be present. This method certainly gives an excellent exposure; but when it is indicated one may find that spinal fusion with additional bone and more immobilization is required to prevent recurrent symptoms. The use of the Wilson type spine plate with bolts through the spinous process (when there is an adequate first sacral spinous process) seems to present definite advantages for obtaining early adequate immobilization of the fusion area and with adequate spinal fusion, including additional bone, is giving very excellent results.]

Horwitz³³⁰ calls attention to a painful deformity observed in the lumbar region of the spine in 3 cases and in the dorsal region of the spine in 1 case following bilateral laminectomy. These patients returned for observation from eight months to fifteen years after bilateral laminectomy involving from two to five vertebrae in which the spinous processes and the laminae on both sides had been removed but the articular facets had been preserved.

They complained of a variable amount of pain, weakness and fatigue in the back, and they presented obvious deformity associated with changes in the intervertebral discs and vertebral bodies in the region of the laminectomy. A similar deformity has been reported by Taylor following bilateral laminectomy in the cervical spine.

. . . Only 5 cases out of 25 bilateral laminectomies were available for study. Four of these 5 cases demonstrated the painful spinal deformity herein described. The fifth patient was as yet asymptomatic.

The author points out:

The use of immediate or delayed spine fusion following laminectomy in the absence of a weakened or diseased vertebral column, has been considered unnecessary by most neurosurgeons. However, an increasing number of orthopedic surgeons are favoring the use of spine fusion in conjunction with the laminectomy.

Horwitz believes that one of the indications for immediate spinal fusion following bilateral laminectomy, the patient's condition permitting, is the prevention of such symptomatic deformities as have been reported by Taylor in the cervical portion of the spine, and in the cases presented. He also feels it is important for patients who are subjected to bilateral laminectomy without immediate spinal fusion to have periodic roentgenograms of the spine in order to ascertain the development of spinal deformity and of secondary changes in bone and soft tissue. He points out that delayed spinal fusion in such cases is technically more difficult than fusion performed at the time of laminectomy and that the vertebral changes which have developed are permanent.

It is possible that hemilaminectomy, as recommended by Taylor, partial laminectomy with preservation of the neural arch, as recommended by Love and Walsh, and the interlaminar approach of Love may obviate the need for spinal fusion, but the use of these procedures, especially of the latter two, is restricted because of their limited exposures. Horwitz points out that symptomatic spinal deformity may appear and preexisting spinal deformity may become aggravated following

330. Horwitz, T.: Structural Deformities of the Spine Following Bilateral Laminectomy. *Am. J. Roentgenol.* 46:836-840 (Dec.) 1941.

bilateral laminectomy in the cervical, thoracic and lumbar regions of the spine, even when the articular facets are preserved. He suggests that such deformities may be prevented by spinal fusion. In cases in which immediate fusion is not done periodic roentgenography is advised for the early diagnosis of secondary changes, and for these he advises fixation by spinal fusion or external fixation.

[ED. NOTE.—As the author points out, an increasing number of orthopedic surgeons are favoring the use of spinal fusion in conjunction with total laminectomy. This operation obviously does weaken the structural elements of the posterior part of the spine, especially in heavy patients or in patients engaged in heavy labor. It certainly is easier to do the spinal fusion immediately after the laminectomy than to do it at a later date. Probably the recurrent symptoms of many of the patients who have undergone laminectomy are caused by structural weakness due to the operation rather than by the original lesion.

It will be interesting to have further reports on other total laminectomies to determine the relative incidence of symptoms as reported in this paper. Probably the onset of symptoms will depend on a number of factors, including the initial lesion requiring bilateral laminectomy (which may well have been an involvement of the disk), other preexisting instabilities or pathologic processes, the weight of the patient and the type of occupation.]

Everett³³¹ reports 3 more cases of injury to the intervertebral disk following lumbar puncture. While this condition has been previously recorded, he stresses this as an important complication following lumbar puncture. Roentgenograms showed definite narrowing of the previously normal intervertebral space at the level where the lumbar puncture was done.

[ED. NOTE.—While this condition has been previously reported, it may be well to stress it as a complication which should be considered in doing routine lumbar punctures.]

Epps³³² also reports a case of degeneration of the intervertebral disk following the lumbar puncture. Roentgenograms showed definite collapse of the intervertebral disk. The process appeared to be an aseptic degeneration. This is a short article and merely reports another case.

Simon³³³ points out that since neither healing nor prevention of the pronounced and fixed kyphosis in kyphosis dorsalis juvenilis is possible except in the primary stage of the disease, an early diagnosis is of the utmost importance. He states that most authors have observed the disease in patients between the ages of 15 and 22 years, while some of his were observed much earlier in the disease.

Following the theory of Schneider that there is some relationship between the diseases of the epiphysis and vitamin-A deficiency, the eyes of all the children were examined for hemeralopia and xerophthalmia. It was found that most of the children with kyphosis dorsalis juvenilis suffered from slight hemeralopia, and xerophthalmia was found in two of the group from nine to thirteen years of age. In a parallel group of children with poor posture only practically no hemeralopia and no child with xerophthalmia was found.

The blood serum of these children was examined for carotene beta and vitamin A, and it was found that most of the children with kyphosis dorsalis juvenilis showed a lack or deficiency of vitamin A. In the blood-serum test for vitamin A the average for the younger group with kyphosis dorsalis juvenilis was 5 international units, and for the older group 130; the average for the total group with poor posture only was 85 international units (without essential dif-

331. Everett, A. D.: Lumbar Puncture Injuries, *Proc. Roy. Soc. Med.* **35**:208-210 (Jan.) 1942.

332. Epps, P. G.: Case of Degeneration of Intervertebral Disc Following Lumbar Puncture, *Proc. Roy. Soc. Med.* **35**:220-221 (Jan.) 1942.

333. Simon, R. S.: Diagnosis and Treatment of Kyphosis Dorsalis Juvenilis (Scheuermann's Kyphosis) in Early Stage, *J. Bone & Joint Surg.* **24**:681-683 (July) 1942.

ference between the younger and older children). In the test for carotene beta, the average for the younger group of those with kyphosis dorsalis juvenilis was found to be 0.039 milligrams per 100 cubic centimeters of blood serum, and for the older group, 0.046; the average for the total group of those with poor posture only was 0.033.

Since roentgenographic examination of such young patients never shows the pronounced symptoms of the disease, the proof of vitamin-A deficiency is an important aid for early diagnosis. Moreover, if vitamin-A deficiency exists in older patients it demonstrates that the active period of the disease has not passed.

Treatment of kyphosis dorsalis juvenilis in the early stage is based primarily on rest for the diseased spine. This is achieved by a plaster-of-Paris corset, which is worn for six months; wearing this corset, it is possible for the child to attend school. In addition, the child is given 40,000 international units of vitamin A daily for three months.

CONCLUSIONS

1. Kyphosis dorsalis juvenilis (Scheuermann's kyphosis) may be seen between the ages of fifteen and twenty-two years, but it may begin as early as eight or ten.
2. Proof of vitamin-A deficiency is an important supplementary aid in the early diagnosis of the disease.
3. Vitamin-A deficiency in older patients is a probable sign that the disease is still active.
4. Children in the early stage of the disease should be excluded from physical exercises, should be given vitamin A, and should wear plaster-of-Paris corsets.

[ED. NOTE.—While vitamin A deficiency may be a factor in the development of kyphosis dorsalis juvenilis, it should be pointed out that this deficiency may be only a concomitant occurrence and not the causative factor in this condition. The possibility that deficiency of other substances, such as vitamin D and gonadal or endocrine factors, is important in this condition must still be considered.]

Rees and Murphy³³⁴ believe with Scott that spondylitis adolescens is an inflammatory arthritis of the spine of infective origin and that the Marie-Strümpell syndrome, Bechterew's spondylitis and *spondylose rhizomélisque* may be classified under the term spondylitis adolescens. They point out its common occurrence and discuss the pathologic change, roentgenographic appearance, symptoms, differential diagnosis and roentgenotherapy. They report 7 cases in which it was treated by roentgenotherapy with definite improvement. The patients were 18, 23, 24, 34, 16, 24 and 28 years old respectively. Rees and Murphy conclude that the earlier the patient is treated in the course of the disease the better will be the result obtained with roentgenotherapy, particularly if treatment can be given in the prespondylitic period. They also suggest that the patient should be hospitalized for roentgenotherapy, as it would otherwise require considerable travel with additional trauma. They also advise that the treatments be taken regularly, approximately twice a week. A table indicating locations and dosages for roentgen treatment is included.

[ED. NOTE.—The conclusions seem to agree with those of most authors who have reported on roentgenotherapy for spondylitis.]

XII. CONDITIONS INVOLVING THE LOWER PART OF THE BACK

PREPARED BY FRFMONT A. CHANDLER, M.D., CHICAGO

Papers on pain in the lower part of the back and sciatica published during the past year again emphasize the importance of the herniated intervertebral disk. Experience with this entity is mounting, and the clinical picture is becoming more

334. Rees, S. E., and Murphy, W. Roentgenotherapy of Spondylitis Adolescens, Northwest Med. 41:164-166 (May) 1942.

clearly defined. According to Dandy,³³⁵ a history of pain low in the back with sciatica which is accentuated by coughing or sneezing is almost pathognomonic of a ruptured disk, and all other refinements of diagnosis are unnecessary. Even the physical examination may be dispensed with. He points to the fact that he found the ruptured disk in 349 of 350 cases. The single patient whose disease was misdiagnosed had a tumor of the spinal cord. [ED. NOTE.—A follow-up study of this remarkable series should be forthcoming, for it is possible that other surgeons have seen some of the patients subsequently and might add items of interest.] Dandy cures the cavity left by the removal of the disk. He considers fusion unnecessary.

In another paper³³⁶ Dandy stresses the serious sequelae resulting from delay in operative treatment. Cases of pressure necrosis of the cervical cord and subsequent death, permanent paralysis from extrusion of a disk in the thoracic region, and permanent sensory and motor damage with continued sciatica and impairment of vesical function from herniation in the lumbar portion of the spine are reviewed. He concedes that iodized oil is of advantage when there is involvement of the spinal cord. The use of such contrast mediums is not indicated for rupture of a lumbar disk, because with rare exceptions the diagnosis can be made with more accuracy and certainty without it.

Craig³³⁷ states that intermittent attacks of pain are considered an outstanding diagnostic point in the history of patients with protruded intervertebral disks. Paresis was found in 20 per cent of the cases from the Mayo clinic, sensory loss in 18 per cent and no neurologic changes in 8 per cent. Increase of pain on coughing or sneezing was found in 67 per cent. The achilles tendon reflex was lost or diminished in 63 per cent of the patients who had lesions of disks at the lumbosacral junction, in 37 per cent of those with lesions at the fourth interspace and in 52 per cent of those with lesions at the third interspace. The patellar reflex was reduced or absent in 49 per cent of the patients with lesions at the third interspace, in 20 per cent of those with lesions at the fourth interspace, and in 9 per cent of those with lesions at the lumbosacral junction. The total protein content of the spinal fluid was over 40 mg. per hundred cubic centimeters in 61 per cent of the cases. Craig favors roentgen examination with air as a contrast medium and considers a small hemilaminectomy the most suitable operation. Statistics from the Mayo Clinic show that an increasing number of spinal fusions are being carried out along with the laminectomy. The percentage of cures subsequent to operation is definitely higher in the group of patients to whom compensation was not available. The fusion operation should probably be done when there is spondylolisthesis or spondylolysis, congenital deformity or hypertrophic arthritis. Narrowing of the interspace alone is not considered an indication for adding fusion to laminectomy.

Kaplan, Bender and Sapirstein³³⁸ report 4 cases of tumor of the cauda equina in which neurologic signs were absent and unilateral sciatica was the only symptom. They find that myelography is essential for diagnosis.

335. Dandy, W. E.: Recent Advances in Diagnosis and Treatment of Ruptured Intervertebral Disks, *Ann. Surg.* **115**:514-520 (April) 1942.

336. Dandy, W. E.: Serious Complications of Ruptured Intervertebral Disks, *J. A. M. A.* **119**:474-477 (June 6) 1942.

337. Craig, W. M.: Role of Protruded Intervertebral Disk in Production of Low Back and Sciatic Pain, *Rocky Mountain M. J.* **39**:98-101 (Feb.) 1942.

338. Kaplan, A.; Bender, M. D., and Sapirstein, M.: Sciatic Pain: Its Significance in the Diagnosis of Cauda Equina Tumors; Report of Four Cases, *J. Bone & Joint Surg.* **24**:193-199 (Jan.) 1942.

Love³³⁹ reports an operative mortality of 0.25 per cent in 1,600 cases of injuries to the intervertebral disks sustained in military service. He suggests that paratroopers, pilots of dive bombers and tank drivers wear a snug-fitting belt as a prophylactic measure.

McKenzie and Botterell³⁴⁰ present an excellent article written from the neurosurgical standpoint. The anatomy of the three parts of the intervertebral disks, the cartilage plates, the annulus fibrosus and the nucleus pulposus, is discussed. The annulus is weakest posteriorly just off center, and it is at this point that herniation almost invariably takes place. The authors do not consider trauma alone or trauma plus degeneration wholly adequate in explaining protrusion of the disk and postulate developmental weakness as well. They explain the loss of normal spacing of the intervertebral disks in tuberculosis as due not to destruction of tissue but to the fact that the disk may bulge into the adjacent vertebral body as the cartilage plate becomes eroded. The authors think that intractable brachial neuritis may often be due to spurs or to extruded calcified disks causing pressure on a nerve root and that this pressure should be looked for more frequently. The intermittency of symptoms due to protrusion of the disks is stressed.

The authors have gradually come to the conclusion that about 95 per cent of sciatica is associated with pressure on the root of the first sacral or the fifth lumbar nerve. The diagnosis has been proved in the small percentage of cases in which there was sufficient disability to justify operation and is presumed in the ones in which the patient has been cured by conservative means or has recovered spontaneously. From a review of the neurologic signs due to protruded disks in the lower portion of the spine the authors conclude that the only important syndromes are those due to lesions between the fourth and the fifth lumbar vertebra and between the fifth lumbar vertebra and the sacrum. A lesion of the fourth lumbar disk, causing pressure on the fifth lumbar root, produces numbness or paresthesia of the inner side of the foot, a normal or diminished ankle jerk and weakness of the dorsiflexor muscles. A lesion of the fifth disk affects the first sacral root and results in numbness or paresthesia of the outer side of the foot, absence of the ankle jerk and weakness of the plantar flexor muscles. A neurologic analysis of their cases showed that when the extrusion was from the fourth disk there were no reflex, sensory or motor disturbances and that when it was from the fifth disk the ankle jerk was absent. They were unable to distinguish between lesions of the fourth or the fifth disk in about 15 per cent of the cases. On the basis of their observations they suggest that exploration may be done without preliminary myelography. They favor conservative treatment first for most patients. For simple sciatica they suggest removal of the disk alone. They believe that when there is much pain in the back spinal fusion is usually advisable, particularly in younger patients.

Overton³⁴¹ presents a good summary article with many useful details and true principles concerning the diagnosis and differentiation of the various causes of pain low in the back and sciatica, but it really contributes nothing new. The local anatomy is reviewed, the causes of pain low in the back and sciatic pain are outlined, the points of a good history are set forth in detail, and a list of fourteen physical signs to look for is given. Many of the standard manipulative tests are detailed.

339. Love, J. G.: Injuries of Intervertebral Disk in Military Service, *War Med.* 2:403-409 (May) 1942.

340. McKenzie, K. G., and Botterell, E. H.: Common Neurological Syndromes Produced by Pressure from Extrusion of Intervertebral Disk, *Canad. M. A. J.* 46:424-435 (May) 1942.

341. Overton, L. M.: Sciatic Syndrome, *Am. J. Surg.* 56:300-307 (April) 1942.

and the differential diagnosis of a number of entities, including gout and osteoporosis, is discussed briefly. Myelography with iodized poppyseed oil is favored for localization of protruded disks.

Le Cocq³⁴² reports a case of sciatica due to aneurysm of the sciatic artery. The patient was a man of 68 who had pulsating sciatic pain and a visible and palpable pulsation of the right buttock synchronous with the heart beat. At operation an aneurysmal sac the size of a small orange was found in the sciatic artery. It was removed with good symptomatic results. The cause of the aneurysm was considered to be an atheromatous degeneration of the arterial wall.

XIII. CONDITIONS INVOLVING THE KNEE JOINT

PREPARED BY RALPH K GHORMLEY, MD, ASSISTED BY H HERMAN YOUNG, MD,
W H BICKEL, MD, PAUL R LIPSCOMB, MD, AND
JUAN RUIZ, MD, ROCHESTER, MINN.

Efskind³⁴³ reviews an experimental study of the anatomy and histology of the knee. Among his conclusions should be noted that normally the synovial membrane shows distinct signs of cellular degeneration and regeneration. After synovectomy the regeneration is brought about by slightly differentiated mesenchymal cells in the connective tissue membrane. The cells of the synovial membrane do not have any capacity for formation of fibroblasts or phagocytic cells. There is an abundance of phagocytic cells in the subsynovial tissue, and Efskind suggests that the joint capsule may belong to the reticuloendothelial system.

Roentgenography of the Knee.—Wiberg³⁴⁴ has found that the femoropatellar joint is best projected in a roentgenogram at 40 degrees of flexion. His study led to some conclusions regarding normal patellas, luxation of the patellas, chondromalacic patellas and arthritis deformans. By means of a detailed roentgenographic study, specially prepared specimens and a necropsy series of 25 knee joints frozen in different positions of flexion, he showed that in certain positions contact between the patella and the femoral condyle takes place over a comparatively small cartilaginous surface and that such extra stress is likely to lead to chondromalacia.

Lagomarsino and dal Lago in 1941³⁴⁵ and in 1942³⁴⁶ again review the subject of pneumoroentgenography, concluding that a preoperative diagnosis of the types of internal derangement can be made.

The Patella—Jones and Hedrick³⁴⁷ summarize and classify the various patellar anomalies that are encountered and are occasionally confused with fractures. They describe six types of anomaly, the first being a conical or triangular projection at the upper and outer quadrant of the patella. The other five types represent types of bipartite patella, the first type, which is the most common one encountered,

342 LeCocq, J F. Sciatica from Aneurysm of Sciatic Artery, *Northwest Med* **41**:121-122 (April) 1942.

343 Efskind, L. Experimental Study of Knee Joint Capsule. Histology and Pathology of Synovial Membrane, *Acta orthop Scandinav* **12**:214-266, 1941.

344 Wiberg, G. Roentgenographic and Anatomic Studies on Femoropatellar Joint, with Special Reference to Chondromalacia Patellae, *Acta orthop Scandinav* **12**:319-410, 1941.

345 Lagomarsino, E H., and dal Lago, H. Sign of Separation of Anterior Cornu of Semilunar Cartilage in Pneumoroentgenography, *Rev ortop y traumatol* **11**:106-123 (Oct) 1941.

346 Lagomarsino, E H., and dal Lago, H. Pneumoroentgenography of Knee, *Rev ortop y traumatol* **11**:192-216 (Jan) 1942.

347. Jones, H C., and Hedrick, D W. Patellar Anomalies. Roentgenologic and Clinical Considerations, *Radiology* **38**:30-34 (Jan) 1942.

being a small fragment at the upper and outer quadrant. The second type is characterized by a vertical fissure usually observed in the lateral quadrant of the patella. There are also the rarer varieties of U-shaped patellas with a small fragment between the two arms of the U. Another type shows a transverse fissure at the lower pole, and the last type is characterized by a linear fracture at the lower pole which appears to be almost in contact with the lower margin of the patella.

Whether the multipartite patella is the result of failure of union of separate ossification centers or the result of localized osteochondritis is still a question. Jones and Hedrick believe that if it is due to osteochondritis the patella should show some evidence of end results similar to those observed in osteochondritis, namely, ultimate healing and union with the main fragment. These are not observed, and therefore, in their opinion, osteochondritis is not the cause. The other hypothesis of origin of multipartite patella is that there is a failure of union of separate ossification centers. In the differential diagnosis of patellar anomaly and fracture the history is all-important. When a fracture is present, the fracture line is usually roughened, whereas with the anomaly the line is smooth. In the anomalous patellas the adjacent surfaces of the fragments are separated fairly uniformly throughout their entire length, while after fractures the space intervening between the fragments is of varying width.

Girardi³⁴⁸ studied the patellas of dogs and found that after excision in these animals there were diminished active movement in the knee, changes in the cartilaginous surfaces and atrophy of the extensor muscles. He agrees with De Vriese that the patella represents the proximal portion of an osseous element intermediate between the tibia and the fibula.

Houkom³⁴⁹ reviews the results of surgical treatment of 27 dislocating patellas from the New York Orthopaedic Dispensary and Hospital. He did not find any definite causative factor. All his patients were female. In 20 cases he classified the deformity as adolescent, in 4 as congenital, in 2 as due to knock knee caused by a fracture in infancy and chondrodysplasia and in 1 as due to residual poliomyelitis. There were no cases of traumatic dislocation. Twenty-two transplants of the tibial tubercle were done, with the following results: 50 per cent excellent, 40 per cent good and 10 per cent poor. In 12 cases fascial structures were cut at the same time as the transplantation was done, with the same percentage of excellent, good and poor results. The medial capsule was plicated in 8 cases, and in 9 supracondylar osteotomy was performed, with 2 excellent, 5 good and 2 poor results.

Pellegrini-Stieda Disease.—Two papers (Hansa³⁵⁰; Kulowski³⁵¹) are devoted to Pellegrini-Stieda disease. [ED. NOTE.—Kulowski's paper is a carefully prepared review of the subject and should be read by any one interested.]

Wounds and Injuries of the Knee.—Mauck³⁵² studied 587 cases of severe acute injuries to the knee, chiefly among athletes and industrial workers. The conclusions drawn are that the primary damage is usually to the ligamentous structures

348. Girardi, V. C.: Experimental Patellectomy in Dogs, *Rev. ortop. y traumatol.* **11**:257-274 (April) 1942.

349. Houkom, S. S.: Recurrent Dislocation of the Patella: Study of End Results in Twenty-Seven Cases, *Arch. Surg.* **44**:1026-1037 (June) 1942.

350. Hansa, W. R.: Sequel of Knee Ligament Strain: Pellegrini-Stieda's Disease (Metacondylar Traumatic Osteoma), *Nebraska M. J.* **27**:62-64 (Feb.) 1942.

351. Kulowski, J.: Post-Traumatic Para-Articular Ossification of Knee Joint (Pellegrini-Stieda's Disease), *Am. J. Roentgenol.* **47**:392-404 (March) 1942.

352. Mauck, H. P.: Severe Acute Injuries of the Knee, *Am. J. Surg.* **56**:54-63 (April) 1942.

then placed in extension in a circular plaster cast. Plaster is applied over stockinet only, with thin felt strip padding about essential bony points. The patient then is urged to walk as much as possible and practice quadriceps exercises at as nearly hourly intervals as possible for four weeks. The cast then is removed and the natural exercise of the extremity encouraged. Murray prefers not to use any physical therapy but depends on active motion of the joint by the patient. Three hundred and sixteen clinically certain injuries of the meniscus so treated healed completely without operation and without recurrence. He felt that had immobilization been practiced in these cases without the emphasis on use and exercise as the essential feature of the treatment, there would have been a relative instability of the knee with secondary lesions of the joint leading to prolonged disability.

When operation must be performed, the patient is instructed in quadriceps muscle exercises, which he carries out for two days prior to operation. After operation a moderately firm pressure dressing is applied for twenty-four to forty-eight hours, but patients start quadriceps muscle exercises at the end of twenty-four hours. When postoperative contraction of the quadriceps muscle is difficult to initiate, it is aided by a Smart coil to give rhythmic contraction. Voluntary bending of the knee is started when the pressure bandage is removed. The patient is up in a chair on the fourth day, is walking with crutches on the fifth or sixth day and usually leaves the hospital about the ninth day. Quadriceps muscle exercises are continued during the entire convalescence. In Murray's opinion, keeping a patient on crutches, deluging him with physical therapy and requiring postoperative immobilization of the knee joint are all conducive to delay of functional and economic rehabilitation.

The second complicating factor entering the discussion was the question of incision used. Murray has come to the conclusion that a small parapatellar incision is unwise because of the proved inability to make the diagnosis of a lesion of the meniscus as the sole pathologic condition present. In 70 per cent of the cases there have been at least two lesions, and in more than half of this 70 per cent there have been anywhere from three to eleven lesions in the joint. Murray now uses a long internal or external parapatellar incision running from the top of the quadriceps pouch to below the tibial margin. The patella then is retracted, and when the joint is flexed the entire joint is exposed. In Murray's opinion, it is only by this method that the joint can be examined completely enough to ascertain what condition is present. He has not found it necessary to repair the anterior crucial ligament in order to restore stability to a knee joint, although in 8 per cent of the cases the anterior crucial ligament was found completely torn and in 6 per cent partially torn. In general, Murray believes that injuries of the crucial ligament are handled best by intensively striving to restore muscular tone and volume and that operative repair should be reserved for those cases in which this is impossible.

The third factor in the discussion was the use of a tourniquet. Murray believes that the use of a tourniquet enforces anoxemia of the extremity below it and that in an extremity already compromised by loss of muscle tone this anoxemia is damaging. In order to alleviate bleeding as much as possible at the time the operation is performed, the patient is placed in the high Trendelenburg position with the knee joint just distal to the foot piece in the table. This effectually drains the venous circulation. When the incision in the skin is made, the bleeding points are surprisingly few in comparison with those encountered when the patient is in the flat position. They are dealt with by clamp and cautery. Towels then are clipped to the wound, incision through the capsule is made and the bleeding points are treated similarly. The synovial membrane is then opened, the patella retracted

and the foot piece of the table dropped, the thigh being left in the Trendelenburg position with the knee flexed at right angles. After operation on the interior of the joint, the knee is again extended, the patient is lowered from the Trendelenburg position to the flat position and any additional bleeding points are dealt with. In closure of the wound, the synovial membrane is left unsutured so that if any oozing occurs the fluid may escape from the joint into the surrounding tissue. A moderately firm cotton pressure bandage or Ace bandage is applied over the dressings.

Murray states that since such a procedure was adopted he has had fewer post-operative collections of fluid in a joint and less difficulty in initiating rehabilitation of the muscles. In his series of 315 cases there were but 3 postoperative infections. Two of these were in knee joints subjected to diagnostic injection of air preceding operation and occurred seven or eight years before the report. In the third case a streptococcic infection occurred during an epidemic of 5 infections of clean wounds in the service. All 3 patients recovered but with marked limitation of function.

Henderson, in the discussion, says that some of the points mentioned by Murray are controversial, such as the use of the tourniquet and the length of time required for the operation. Henderson, in reporting 343 operations performed up to 1934, with the addition of 173 cases since that time, states that in the 1934 group there was complete relief in 77 per cent, improvement in 14.4 per cent and no relief in the rest. He believes, unlike Murray, that many unsatisfactory results following removal of the meniscus are due to the fact that the anterior crucial ligament was torn or stretched at the time of the injury and that the symptoms which persisted were due to lesions of that ligament.

Graham³⁵⁷ reviews 128 cases in which arthrotomy was performed for internal derangement of the knee. The operations were done on soldiers in an Australian general hospital. Because of the dust and heat, encircling bandages and pads were omitted and a light acriflavine gauze dressing was sutured over the wound. More effusion and hemarthrosis than without encircling bandages were noted, but in only 2 cases was aspiration performed. Quadriceps muscle exercises were started in twenty-four hours. The average time from operation to return to light duty was forty-two and a half days. Persistent effusion was an indication for, not a contra-indication to, active function of the quadriceps muscle. Stout³⁵⁸ reviews the results of operations on the knee joint in a hospital for members of the New Zealand expeditionary force. Of the patients whose cartilages had been injured, 69.7 per cent returned to full duty and 16.3 per cent to base duty and 14 per cent were sent back to New Zealand.

Mandl³⁵⁹ reports on a group of 840 cases of lesions of the semilunar cartilage. Thirty per cent of the series lacked the history of severe trauma, and Mandl believes that most tears of the semilunar cartilage are pathologic fractures. Rupture of the medial meniscus was eight times more frequent than that of the lateral meniscus, but cysts were more common in the lateral cartilage. Mandl recommends surgical removal in all cases of torn semilunar cartilage. He recommends a short longitudinal incision and local anesthesia and never uses a tourniquet

357 Graham, R V Preliminary Report on Internal Derangements of the Knee Joint Treated at an Australian General Hospital, Australian Imperial Force Abroad, to May 31, 1941. Australian & New Zealand J. Surg **11**:185-196 (Jan) 1942

358 Stout, T D M Rupture of Semilunar Cartilages of Knee Joint, Osteochondritis Dissecans and Hallux Valgus and Rigidus Results of Operative Treatment and Significance of These Disabilities in Second N Z E F, New Zealand M J **41**:130-133 (June) 1942

359 Mandl, F Observations and Problems on Operation for Lesions of Semilunar Cartilage, J Internat Coll Surgeons **5**:63-68 (Jan-Feb) 1942.

Dunlap³⁶⁰ has modified the Lowe-Breck knife for removing semilunar cartilages, making it more curved and making the cutting edge V shaped instead of U shaped.

Hauser³⁶¹ reports an average of 80 to 90 per cent cure after operation for tear of the semilunar cartilages. He reports 4 cases illustrating the fact that loose bodies derived from the semilunar cartilages may be present in the joint. These loose bodies are pieces of cartilage that are lying free within the joint and may occur at the time of initial injury or may occur at a later date with repeated trauma to the cartilage. Unless the joint is examined thoroughly, some of these "joint mice" may be missed and produce an unsuccessful end result. Hauser believes that removal of the entire meniscus is indicated in all cases of fractured semilunar cartilage in order to make sure that all of the cartilaginous tissue has been accounted for and that some does not remain in the joint.

Deformities of the Knee.—Abbott and Gill³⁶² review the cause and treatment of valgus deformities of the knee occurring as a result of injury of the lower femoral epiphysis in childhood. The epiphysis fuses in its lateral position but continues to grow on the medial side and thus causes the valgus deformity of the knee. The degree of valgus depends on the exact location of the injury; the more lateral the injury, the greater the deformity because of the greater pivoting action. Likewise the younger the child at the time of injury, the greater the deformity. The longitudinal downgrowth of the medial condyle never equals that on the normal side, and actual shortening occurs. When the medial side of the cartilage fuses, the deformity is fixed. In addition to actual loss of length there is decreased functional length because of the valgus of the knee. There may also develop a secondary varus deformity of the upper end of the tibia, which is compensatory. The development of the femoral articular surfaces is undisturbed, but the plane of motion in relation to the shaft of the femur is altered; thus motion of the knee may be entirely normal. The soft structures on the lateral side of the thighs, including the peroneal nerve, become relatively short, and may constitute an obstacle to the correction of the deformity.

The problem of suggested treatment for far advanced deformity is to secure complete correction with as much increase of the length of the leg as possible. Normal function of the knee should be maintained, and any residual inequality of the length of the legs may be eliminated by leg lengthening or shortening operations. The procedure may be varied in two ways: 1. A triangular section of bone with its base facing inward may be removed from the medial side of the femur. This constitutes cuneiform osteotomy. 2. Osteotomy may be performed at the same level but wedged and held open on the lateral side with a bone graft from the ilium. The latter type of osteotomy gains more length than cuneiform osteotomy. Abbott and Gill stress the importance of roentgenograms of both legs and of making a plan ahead of time as to the angle of the osteotomy and how much correction is to be done. A similar osteotomy may be necessary to correct the virus deformity of the upper end of the tibia.

The greatest obstacle to full correction is the shortness of the peroneal nerve. Abbott and Gill use pin fixation in doing osteotomy. One pin holds the iliac graft

360. Dunlap, K.: Method for Complete Removal of Semilunar Cartilage, *J. Bone & Joint Surg.* **24**:929-931 (Oct.) 1942.

361. Hauser, E. D. W.: Loose Body of Knee Derived from Meniscus, *J. Bone & Joint Surg.* **24**:307-310 (April) 1942.

362. Abbott, L. C., and Gill, G. G.: Valgus Deformity of Knee Resulting from Injury to Lower Femoral Epiphysis, *J. Bone & Joint Surg.* **24**:97-113 (Jan.) 1942.

in place, and the other two pins hold the knee in the corrected position. If full correction is not possible at the time of the operation owing to tightness of the peroneal nerve, the deformity is corrected as much as possible, the graft held in place with pins and a spica cast applied. Three weeks later the pin holding the graft is withdrawn and the cast wedged to correct the deformity further. It is possible to gain about 2 inches (5 cm.) in some cases by double osteotomy. For growing children the authors advocate repeated osteotomy if necessary, to prevent the development of severe deformity, the final correction being done at the time of the closure of the epiphysis. For the growing child osteotomy should be performed before the medial condyle has overgrown the lateral condyle by more than $\frac{3}{4}$ inch (2 cm.). Repeated osteotomy in childhood gives added length with each operation. The deformity is never allowed to become severe, and correction is thus obtained more easily. Abbott and Gill advocate arrest of growth of the corresponding epiphysis of the normal leg before the normal femur has overgrown the involved femur by 2 inches (5 cm.), provided the final height is satisfactory with this loss of growth.

Irwin³⁶³ reviews the deformity of genu recurvatum which sometimes follows poliomyelitis. He has found two types. The first is caused by loss of power of the quadriceps muscle and inability to lock the knee in extension. Structural changes of the bone obeying Wolff's law develop. The condyles of the femur become elongated and the angle of the tibial plateau becomes more acute than normal. The second type is caused by weakness of the calf and hamstring muscles, and the soft tissue becomes stretched. Operative treatment is successful only for the first type. Irwin corrects the deformity of the bone by wedge osteotomy of the tibia and fibula just below the epiphysal line. The proximal tibial fragment is controlled by a Kirschner wire incorporated into the spica cast. The second operation attacks the cause of the deformity by transplantation of the hamstrings into the patella.

Fitzgerald³⁶⁴ describes a method of overcoming flexion deformities of the knee by applying modified Russell traction. The leg is placed on an adjustable Braun splint with a pin through the os calcis and a sling just below the knee. Russell's traction is applied with a 7 pound (3.2 Kg.) weight. The foot of the bed is elevated. As the flexion deformity is overcome, the Braun splint is lowered so that the component forces applied to the leg pull in its long axis.

Young³⁶⁵ states that the problem of the fractured femur is the problem of the stiff knee. The stiffness may be due to disuse, immobilization or sepsis or to a combination of these three. Disuse is the most common and important cause and most easily prevented. Young advocates motion within the first six weeks after operation, if possible. He describes a simple mechanical apparatus whereby the patient actively sends the knee against the resistance of a counterpoising weight. In 34 cases of fracture of the femur, 18 patients were treated with early movement of the knee and 16 without early movement of the knee. In the former group there was an average of 115 degrees of flexion at six months, but in the latter there was only 35 degrees of flexion.

363 Irwin, C. E. Genu Recurvatum Following Poliomyelitis. Controlled Method of Operative Correction, *J. A. M. A.* **120**:277-280 (Sept. 26) 1942.

364 Fitzgerald, I. P. Reduction of Old-Standing Dislocation of Knee Joint, *Brit. M. J.* **2**:542 (Nov. 7) 1942.

365 Young, R. H. Prophylaxis and Treatment of Stiff Knee Following Fracture of Femur, *Proc. Roy. Soc. Med.* **35**:716 (Sept.) 1942.

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Blair ³⁶⁶ describes an operation for stabilizing knees having torn crucial and collateral ligaments with four strips of fascia 12 inches by 1 inch (30 cm. by 2.5 cm.), fixed from the tibia and the fibula to the muscles and fascia of the thigh so that two cross at the fixed point of the femoral condyle. Six cases are reported, with 5 good results.

Unusual Lesion of the Knee.—Key and Large ³⁶⁷ report a case of histoplasmosis or reticuloendothelial cytomycosis, a condition caused by *Histoplasma capsulatum* of Darling. Darling discovered the organism in 1906 and pointed out its similarity to the Leishman-Donovan body of kala-azar. This case is the only one in which a joint has been found involved. The clinical diagnosis was a low grade pyogenic or a fulminating tuberculous infection. Amputation was done, but the patient died of pneumonia.

366. Blair, H. C.: Simple Operation for Stabilization of Knee Joint, Surg., Gynec. & Obst. **74**:855-859 (April) 1942.
367. Key, J. A., and Large, A. M.: Histoplasmosis of Knee, J. Bone & Joint Surg. **24**:281-290 (April) 1942.

(To Be Continued)

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